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ABSTRACT

Presented Abstracts from the Thirty Fourth Annual Education Conference of the National Society of Genetic Counselors (Pittsburgh, PA, October 2015)

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Awards Papers

Best Full Member Abstract

Assessment of Complexity Among Cancer, Cardiovascular, General Pediatric/Adult, and Prenatal Genetic Counseling at a Single Institute: A Tool to Improve Efficiencies and Help Guide Patient Volumes

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1. Cleveland Clinic

Increasing demand for genetic counseling necessitates efficiency in practice. However, distinct differences exist between various disciplines of genetic counseling, making it difficult to establish standardized practice methods and patient volume expectations. Genetic counselors (GCs) at Cleveland Clinic developed a data collection tool to track time and 69 activities related to pre-visit, in-person, and post-visit care as well as referral indications. The practice provides cancer, cardiovascular, general, and prenatal services. We hypothesized that the general practice had greater complexity, and thus higher time requirements, than the other three specialties. Over a 6 week period, 12 GCs prospectively tracked data, encompassing 583 patient visits (252 cancer, 103 cardiovascular, 136 general, and 92 prenatal). Data were analyzed comparing general versus specialist GCs. Variables were compared with hierarchical linear models for ordinal or continuous data and hierarchical logistic models for binary data. Descriptive statistics were also utilized. The number of patients seen weekly/1 FTE was: 14.7 (cancer), 8.6 (cardiovascular), 7.3 (general), and 11.8 (prenatal). General GCs completed more pre- and post-visit activities (p=0.011) and spent more time (p=0.009). General GCs reported higher case discussion with other providers (p<0.001), literature review (p=0.026), testing option research (p=0.041), electronic medical record review (p=0.040), insurance pre-authorization (p=0.05), and patient inquiries (p=0.003). Greater redundancy of referral indications was observed by specialty GCs; 66 % of cancer, 44 % of cardiovascular, and 50 % of prenatal patients were referred for 1 of 2 common indications, compared to 16 % of general patients. Establishing patient volumes is a balance between creating access and providing comprehensive care and should include consideration of specialty and variety of indications for referral. These data demonstrate that general GCs may require lower patient volumes than other specialties to allow time for additional pre-/post-visit activities.

Beth Fine Kaplan Best Student Abstract

Assessing Current Practices in Prenatal Genetic Counseling Regarding a Prenatal Diagnosis of Down Syndrome. Phase II: What Does Client-Centered Counseling Look Like in Practice?

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Recent discourse surrounding Down syndrome prenatal testing emphasizes the need for communicating balanced, up-to-date information. The 2011 NSGC "Practice Guidelines for Communicating a Prenatal or Postnatal Diagnosis of Down syndrome" supported genetic counselors in this endeavor. Our group's previous work found that counselors discuss the guidelines' essential concepts almost always while frequency of discussion of lived experience (LE) concepts was most variable. This follow-up study focused on a deeper understanding of factors that contribute to practice guidelines deviations, specifically related to LE discussions. Participants self-identified at completion of our group's 2014 quantitative survey (N=45) were stratified into 3 groups according to their average discussion frequency (high, average, low) of LE concepts. Semi-structured interviews (N=8) focused on 3 scenarios in which a patient was seen in-person for a prenatal diagnosis of Down syndrome and was (1) unsure, (2) planning to terminate or (3) planning to continue the pregnancy. Questions focused on what counselors did/did not communicate regarding the diagnosis and their rationale. Transcripts were independently coded holistically by 3 group members in an iterative process to identify process-related codes. The group coalesced the codes into themes related to the study objective. Counselor considerations of patients' needs and desires for information were the most significant contributors to deviation from the guidelines during a prenatal Down syndrome diagnosis session. In particular, counselors' concerns about overwhelming the patient and being perceived as unsupportive were recurrent. Our results suggest that genetic counselors strive for a client-centered approach by prioritizing both patients' explicit and implicit informational wants and needs over providing comprehensive information for a prenatal diagnosis of Down syndrome. Deviations from the guidelines were a

consequence of heightened counselor self-awareness regarding a potential negative impact of information giving on the patient.

Platform Presentations

I. Access and Service Delivery I

Psychiatric Genetic Counseling: A Practice Model from the World's First Clinic

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In February 2012, the world's first specialist psychiatric genetic counseling (GC) clinic opened in Vancouver, Canada as a direct result of research, which had demonstrated the benefits of and the need for GC for this population. Genetic counselors (GCl) and other healthcare professionals (HCP) from around the world have come to train at this clinic, indicating the emerging need for a practice model for psychiatric GC. Here, we define the model of practice for psychiatric GC services that has been established in British Columbia, based on prioritization of patient outcomes as the benchmark metrics for value/success. The clinic's one full-time GCl is supervised by a PhD psychiatric geneticist/GCl, supported by a 0.2 full time equivalent clinical secretary (who assists with bookings), and has access to consult with a geneticist and a psychiatrist. The GCl: obtains family histories prior to appointments (45 min), provides GC by telephone, telehealth or in person (at base location or at outreach sites, 100 min); follows up with all patients 1 month after GC (20 min), completes detailed consult reports to referring HCP, and participates in bi-weekly peer-supervision. Full case-load given these activities is 5 patients per week. Learners are present at appointments for 5 months of the year. The clinic accepts self-referrals and referrals from any HCP. Medical records are not routinely sought to confirm diagnoses, instead the GCl trained in psychiatric interviewing to elicit high quality personal and family mental health histories. For patients where a genetic syndrome is suspected, the GCl addresses psychiatric concerns before referring to a geneticist for an assessment and possible genetic testing. An evaluation of patient outcomes after the clinic's first year demonstrated significant increases in empowerment and self-efficacy 1 month post GC, showing that this practice model is effective. In describing the practice model, we aim to allow other services to be informed based on the model we have established.

A Novel Genetic Counseling Service Delivery Model in a Pediatric/General Genetics Clinic Setting

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1. Beaumont Health, Royal Oak, MI

A novel genetic counseling service model in a pediatric/general genetics setting is presented whereby the genetic counselor (GC) and the physician (evaluation and management [E/M]) portions of the visit are separated into 2 distinct visits (referred to as the GC visit and the E/M visit, respectively). In this new model, patients are seen first by the GC with the E/M visit occurring at a later date; a GC visit is required prior to any E/M visit. We began incorporating this system in April of 2014, with full implementation by the end of 2014. This new model has increased access to our services by decreasing the wait times for an initial visit from 4 (or more) months to 2 months, allowed for triage at the GC visit rather than by phone, and allowed more flexibility in scheduling appointments for both services. In addition, physician time is used more efficiently, as some patients have only required GC visits and the E/M visits are shorter in duration. This change allows the physician to see more patients or attend to other clinical activities without increasing the overall clinic time. Lastly, because the GC visit does not involve a physical examination, minor patients do not need to attend this visit; this has been especially helpful to families with young children (who distract the parents) and in older children (whose families do not wish to take them out of school). Disadvantages in this model include added costs to the patient/family (since insurers generally have not covered the GC visit) and the inconvenience of having 2 appointments rather than one. Overall, this model has been well received by patients and providers and provides a means to increase access and efficiency in genetics clinics.

Role for Genetic Counselors in Creating Clinical Decision Support Messages for Genomic Results

S. Aufox[1], M. Smith[1]

1. Northwestern University

It is anticipated that as the cost of genomic sequencing decreases, there will be an increase in the use of genomic testing. While studies have shown that many genetic counselors believe that they should be involved in pre/post-test discussions as well as reporting genomic results, the current model for providing genetic counseling for genomic testing is neither practical nor scalable. Furthermore, it is speculated that most of these tests will be ordered by clinicians without the involvement of genetic counselors. There are concerns about how genomic results will be used and understood by clinicians, since many clinicians are not knowledgeable about, or comfortable with, conveying the issues surrounding genomic information to their patients. Using Clinical Decision Support (CDS) messages in the electronic health records (eHR) can assist clinicians with the clinical application of genomic results. CDS messages, which are designed to improve clinical decision making, are becoming a useful tool in patient care and are an area where genetic counselors can assist clinicians to use and understand genomic test results. Messages can be triggered based on specific test results or patient characteristics, and have been shown to improve clinician performance. Genetic counselors are perfectly positioned to create content and recommendations for genomic-related CDS messages. Genetic counselors at Northwestern University, together with a team that included eHR programmers, designed messages and recommendations tailored to specific pharmacogenomic and genomic results. These messages triggered during patient appointments or when prescribing medications, and were accessible through a sidebar menu in the eHR. The genetic counselors monitored issues that arose during the CDS rollout and made adjustments to help clinicians better manage results. With the healthcare focus shifting to precision medicine and personalized patient care, genetic counselors can be a key player in assisting clinicians to use genomic information by being involved with CDS development and application.

Leveraging Data to Provide Financial Justification for Additional GC FTE and Resources: Turning a Pilot into Reality

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As part of Seattle Children's laboratory utilization management (UM) program, an institutional policy requiring preauthorization for all genetic tests was implemented in 2012. However, a clear process to carry out the policy was not defined. Despite dedicated hospital resources, including insurance processing specialists, genetic nurses, and clinical and

laboratory genetic counselors (GCs), a typical test preauthorization request takes many months to complete and involves unnecessary communication hand-offs. We hypothesized that early involvement of a laboratory GC in the preauthorization process would lead to improved turn-around time, reduced staff/provider frustration, and would ensure the correct genetic test variables were submitted with the authorization request, including robust medical necessity documentation. A 5-week pilot was conducted in October 2014 using an electronic preauthorization communication order and laboratory GC involvement to facilitate efficient submission of necessary and correct data to the insurance processing specialists. Time studies were conducted to capture baseline and pilot metrics. The average request turnaround time was halved for the 99 requests submitted during the pilot. There were measureable reductions in collective provider and staff time and rework related to the process. Using this data, we estimated staffing requirements for pilot expansion. A business proposal submitted to hospital leadership included estimates of cost-savings associated with having the right person doing the right work (optimize qualifications), cost-avoidance of preauthorization work related to inappropriate/unnecessary requests, and cost-avoidance related to prevention of inappropriate/unnecessary tests. The improved efficiencies and quality related to use of a laboratory GC in a standard process result in sufficient cost-savings to justify the additional FTE required for pilot expansion. A phased expansion of the new genetic testing preauthorization process is proposed, with plans to hire additional FTE to support full expansion.

Partnering with Patient Services Associates to Streamline Insurance Authorization Requests for Genetic Testing

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1. University of Michigan
2. Illumina

Introduction: Genetic testing insurance coverage varies by insurer, plan, and hospital contracts. Ascertaining coverage is a multi-step process, often requiring genetic counselors' (GCs) input and time. Given the increasing use of genetic testing, our goal was to develop a streamlined work-flow for obtaining insurance authorization, including delegation of tasks from GCs to patient services associates (PSAs). Methods: The University of Michigan Cancer Genetics and Medical Genetics Clinics partnered with an industrial engineer to map the genetic testing authorization process. The industrial engineer observed and interviewed our clinics' PSAs and GCs and then together we brainstormed ways to increase efficiency, decrease redundancy, and reassign tasks. Results: This evaluation identified tasks that could be completed by PSAs and the following work-flow changes were made: 1) instituted having PSAs send a pre-clinic email to the GCs noting for each patient whether genetic testing was a covered benefit, needed pre-authorization or coverage would be decided after testing 2) created a shared database where GCs enter genetic test information needed by the PSAs to request authorization and the PSAs record when the request was made and outcome 3) instituted including the information needed by insurers to determine genetic testing coverage in the clinic visit summary letter, eliminating the need for a separate letter of medical necessity and 4) instituted PSAs contacting patients about insurers' decisions. As a result of these changes, time is not taken during clinic to ascertain patients' genetic testing coverage and the PSAs are responsible for insurance authorization requests. Utilization of the shared database has notably reduced GCs/PSAs emails and phone calls. Conclusion: Workflow changes instituted through GC partnership with the industrial engineer and PSAs made it more efficient to request and track genetic testing insurance authorizations, enhanced communication, and reduced tasks done by genetic counselors.

Genetic Counselors are Underutilized in Their Professional Capacities

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Introduction: The demand for certified genetic counselors (CGCs) continues to rise, especially with the increasing availability of genetic tests, and recognition of the importance of genomic information in medical care. As the genetic counseling workforce strives to meet these demands, we must consider appropriate utilization of the skills and expertise of CGCs. Methods: Five cancer CGCs in a large academic center underwent a 4-week beeper time study with the goal of obtaining two work weeks of data per CGC. Prior to initiation of the beeper time study, CGCs were queried about daily tasks and a 29-item categorical task worksheet was developed. Beepers were programmed for random alerts, multiple times throughout the workday; for each alert, CGCs recorded the type of task being performed. Results: 373 total hours were documented over the study period. On average, full time CGCs recorded 89.5 hours each and the part time CGC recorded 15.0 hours. Of the total recorded time, 11 % was spent in "pre-clinic work" (related to next upcoming clinic day), 18 % was spent in clinic, and 22 % was spent in "post clinic work" (related to most recent clinic day). The largest percentage of time, 49 %, was spent doing "office work" which included organizing and filing, printing/faxing and copying, triaging phone calls and patient scheduling. Conclusion: This time study identified multiple areas of underutilization of CGCs, with 49 % of time spent on "office work" that could be delegated to administrative staff, genetic counseling assistants, or student workers. Offsetting these types of tasks to non-CGCs will allow for more time in direct patient care and professional collaborative roles, thus creating the potential to increase clinic volume and reduce appointment wait time. Undertaking a time study provides systematic collection of data which can successfully document the need for administrative staff in an effort to maximize efficiency and appropriate utilization of CGCs.

II. Clinical Care: Cancer

Hereditary Hematological Malignancies: A Hereditary Leukemia Clinic, One Year in Review

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1. The University of Texas MD Anderson Cancer Center

Introduction: Long considered sporadic, hematologic malignancies have rarely been targets for genetic evaluation, even in familial cases. Evidence suggests >10 % of individuals with blood cancers have >=1 first-degree relative with blood cancer, suggesting familial predisposition. Surveillance protocols for these likely under-diagnosed families are not well-established. Many families with increased incidences of hematologic malignancies do not have currently described syndromes, suggesting additional causative genes remain to be identified. Methods: To identify these individuals, a hereditary leukemia clinic was established. Staffed by a leukemia medical oncologist and genetic counselor, the clinic offers genetic counseling, clinical, and research testing for individuals suspected to have predispositions to hematologic malignancy. Over 13 months, 56 individuals were evaluated. Skin biopsies were performed for those with active hematologic malignancy or status-post bone marrow transplant. Further evaluation of families was initiated utilizing next-generation sequencing on a whole exome sequencing protocol. Results: Genetic testing

was performed in 35/56 individuals (62.5 %). 19/56 (34 %) were enrolled in a whole exome sequencing protocol if negative for known susceptibility genes or not suggestive of a described syndrome. Two (3 %) did not undergo any testing. 18/35 who underwent clinical testing (51 %) were tested based on somatic alterations concerning for germline mutations. Testing identified 9/56 (16 %) with germline susceptibility to hematologic malignancy. 6/56 (11 %) had *RUNX1* mutations; one harbored a novel mutation. One individual (2 %) with myelodysplastic syndrome and pulmonary fibrosis was identified to have dyskeratosis congenita but did not meet diagnostic criteria. Two (3.5 %) were identified to have Li-Fraumeni syndrome. Conclusions: Individuals with hereditary susceptibilities to hematologic malignancies are not as rare as previously thought. Clinical evaluation of these patients through genetic counseling and testing is high yield for identifying at-risk families.

Preliminary Results of Expanded Hereditary Cancer Panel Testing: Is More Always Better?

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1. Ambry Genetics

CancerNext (CN) includes 28 genes associated with hereditary melanoma, breast, ovarian, uterine, pancreatic, and colon cancer. CancerNext-Expanded (CN-E) includes 15 additional genes, as it was developed to also encompass paraganglioma/pheochromocytoma and renal cancer. Here we sought to determine if the inclusion of these genes would improve diagnostic yield of CN-E compared to CN and to assess the phenotypes of the CN-E positive patients. Between July 2014 and March 2015, 1,270 individuals were tested with CN-E. Positive and variants of uncertain significance (VUS) rates were compared to CN results from 8,058 individuals tested between March 2012 and March 2015. Clinical data reported by ordering providers was assessed for patients with positive CN-E results. Out of the 1,270 individuals tested with CN-E, 150 had a positive result and 547 had at least one VUS. 26 positive individuals had alterations in CN-E only genes, 14 of whom did not have a personal or family history that would have prompted further testing for these genes. Five of 26 positive results represent atypical mutations including one moderate risk *RET* mutation and 4 *FH* mutations associated with autosomal recessive fumarate hydratase deficiency rather than cancer predisposition. The overall positive rate was similar for CN-E and CN (11.8 % and 11.7 % respectively), however the VUS rate was significantly higher for CN-E (43.1 % vs. 32.7 %; p-value = 2.16×10–13 using 2-sample test for equality of proportions). The diagnostic yield of CN-E is not improved compared to CN. This may be because the genes exclusive to CN-E correspond to rare distinct tumor types, or may be a reflection of a more complex phenotype in patients undergoing CN-E. The relatively low number of individuals found to have mutations in CN-E only genes without suggestive family history (1.1 % of total tested) indicates that the utility of CN-E is most evident in individuals with a personal or family history consisting of a broad spectrum of tumors, including those associated with genes excluded from CN.

Incidence and Spectrum of Germline Mutations in Cancer-Predisposing Genes in Children with Cancer: A Report from the Pediatric Cancer Genome Project

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1. St. Jude Children's Research Hospital

Background: The incidence and spectrum of germ line mutations in cancer-predisposing genes in pediatric oncology patients remains poorly defined. The presence of these mutations has important implications that influence cancer treatment and surveillance for patients and their families. Methods: To gain insights into the frequency and range of cancer predisposing mutations, we analyzed the germ line and tumor genomes of 1,120 pediatric oncology patients by whole genome and/or exome approaches. Mutations were assessed among 565 cancer-associated genes, including 60 clinically relevant autosomal dominant and 29 autosomal recessive cancer predisposition genes. Mutations were classified as pathologic or likely pathologic based on comparison to cancer gene and locus specific mutation databases, *in silico* analyses and literature review. Results: Across the clinically relevant cancer predisposition genes analyzed, pathogenic or likely pathologic mutations were identified in 96 patients (8.6 %), with *TP53* (n=48), *APC* (n=7) and *BRCA2* (n=6) representing the most frequently mutated genes. A single patient was identified with bi-allelic *ATM* mutations. Four patients exhibited germline mosaicism with a mutant allele fraction in normal tissue ranging from 10 to 30 %. Fifty-eight of the 96 patients (60 %) had family history information available, with 21 (36 %) demonstrating a positive family cancer history. Conclusions: Germ line mutations in 60 clinically relevant predisposition genes were found in 8.6 % of pediatric cancer cases. Despite the known association between germline mutations and familial transmission of cancer, family history alone fails to predict the presence of underlying germline mutations in a substantial proportion (64 %) of patients.

Evaluating the NCCN Clinical Criteria for *BRCA1/2* Genetic Testing in Breast Cancer Patients

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Hereditary Breast and Ovarian Cancer (HBOC) syndrome predisposes females with a *BRCA1* or *BRCA2* mutation to an up to 85 % lifetime risk for breast cancer and an up to 40 % lifetime risk for ovarian cancer. It is crucial for individuals with HBOC to be identified to allow for proper screening, management, and identification of at-risk family members in order to reduce mortality. The National Comprehensive Cancer Network (NCCN) has established clinical guidelines for when to recommend *BRCA1/2* testing. A retrospective chart review of 1,123 M.D. Anderson Cancer Center breast cancer patients was performed in order to evaluate the positive predictive values (PPVs) of 14 individual criterion for predicting a *BRCA1/2* mutation. Two criteria had PPVs significantly below 10 %. Only 2 of 115 patients recommended for testing based solely on the criterion of "diagnosed with breast cancer <=45 years of age" tested positive for a pathogenic mutation at a PPV of 1.6 % (0.2–6 %, 95 % CI), which is significantly below the clinical utility cut-off of 10 % (p=0.001). Additionally, 0 out of 37 individuals who underwent testing based on the criterion, "diagnosed with breast cancer at any age with >=2 close blood relatives with breast cancer at any age" tested positive (0–9 %, 95 % CI). Overall, an individual who meets more than one criterion has a PPV of 12 % while those who meet only one criterion has a PPV of 3.52 %, which is significantly below 10 % (p<.0001) for predicting *BRCA1/2* positivity. This data can help provide more personalized risks and anticipatory guidance for patients in their decision to pursue genetic testing.

High Frequency of Germline Mutations Among Unselected Patients Enrolled in a Tumor/Normal Cancer Genomic Sequencing Project

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Introduction: The MI-Oncoseq project sequences tumor-normal pairs to identify therapeutic targets. We aimed to understand the germline variant spectrum in study participants. Methods: Adults (age 18+) with refractory tumors and children (<= age 25) with all tumor types are study eligible. Patients meet with a genetic counselor (GC) at the time of consent to the IRB-approved protocols for discussion of potential secondary germline findings and collection of a cancer focused pedigree. Germline results are reviewed for 161 genes involved in cancer pathways, which are categorized and reviewed by the study team, including a GC. Category 1 includes genes associated with autosomal dominant, high risk cancer syndromes. Category 2 includes genes associated with autosomal dominant, moderate risk cancer syndromes. Autosomal recessive genes are grouped separately. Pathogenic/likely pathogenic (P/LP) variants in the 80 category 1/2 genes are considered for disclosure. Results: Between August 2011 - October 2014, 463/500 enrolled patients (400 adult, 100 pediatric) completed sequencing (92.6 %). 1594 total variants (indels, single nucleotide variants, copy number variants), 631 unique, were identified in category 1/2 genes in 431 patients (mean 3.7 variants/patient). 32 patients had no category 1/2 gene variants. P/LP variants were identified in 20 category 1 genes in 20 patients (*APC*, *BRCA1/2*, *BRIP1*, *DICER1*, *FH*, *MLH1*, *MSH2*, *PDGFRB*, *SBDS*, *SMARCA4*, *TP53*) and 23 category 2 genes in 23 patients (*APC* p.I1307K, *BAP1*, *BARD1*, *CHEK2, HOXB13, MITF, MYH, PALB2*). One patient had P/LP variants in both categories. 255/395 category 1/2 variants of uncertain significance (VUS's) were not previously reported in public databases. 1,159 variants were benign. Conclusion: 9.1 % of patients with cancer referred to a tumor-normal sequencing project, unselected for family history, had a P/LP germline variant associated with a high/moderate cancer risk. This finding highlights the importance of prior genetic counseling about potential germline findings in tumor-normal sequencing and demonstrates the GC role in reviewing and interpreting results.

The Angelina Jolie Boomerang Effect: How are Things Different this Time Around?

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1. UT Southwestern Simmons Comprehensive Cancer Center

The "Angelina Jolie effect" refers to the rise in awareness and uptake of genetics services after her 2013 New York Times op-ed about her decision to undergo genetic testing and (when positive for a *BRCA1* mutation) preventive bilateral mastectomy (PBM). This year, Ms. Jolie wrote about her preventive bilateral salpingo-oophorectomy (BSO). We sought to explore how individuals made meaning of her decisions. We hypothesized that the public would be more supportive of her BSO than PBM and have an increased awareness of genetic counseling and improved genetics knowledge in 2015 vs. 2013.

We performed a content analysis of the online comments to Ms. Jolie's two op-ed pieces for the New York Times (2013, N= 624; 2015, N= 544). Comments represented individuals from 42 states and 37 countries. Two study team members coded comments for emerging themes (inter-rater reliability 90 %).

More people reported a personal or family history of a gene mutation, cancer, or similar surgery in 2013 than in 2015 (18 % vs. 14 %; p<0.001). More individuals expressed direct support for Ms. Jolie's PBM than her BSO (7 % vs. 2 %, respectively; p<0.05). Consistent themes across both op-eds included improved education, bravery, the importance of screening, choice, and not feeling alone or afraid anymore. More comments discussed risk (p<0.001) and femininity (p<0.01) in 2013. More comments equating knowledge with power appeared in 2015 (p<0.001). Although proportions of comments on problems with access to healthcare/resources were similar (13 % vs. 15 %), more comments expressed insurance concerns in 2015 (p<0.001), specifically noting the Affordable Care Act. Twenty comments mentioned gene patents in 2013, compared to 1 in 2015 (p<0.001). These results indicate a need for genetic counselors to be aware of overarching current events in healthcare. For each op-ed, <2 % of comments mentioned genetic counseling. There were also comments demonstrating inaccurate genetics knowledge. This suggests that there are still improvements to be made in educating the public about cancer genetics and our profession.

III. Genetic/Genomic Testing

Genetic Testing for Hereditary Cancer Predisposition: The Impact of the Number of Tests Presented and a Provider Recommendation on Decision-Making Outcomes

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2. National Cancer Institute, National Instutes of Health
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4. Johns Hopkins University Bloomberg School of Public Health

Objective: The abundance of genetic testing options raises questions for genetic counselors when deciding which tests to offer and how to offer them. The objective of this study was to examine how the presentation of a choice can influence clients' decisions about genetic testing for inherited cancer predispositions. Specifically, we wanted to explore how the number of options and the addition of a personalized clinician recommendation might influence the likelihood of a client choosing to undergo genetic testing, the genetic test chosen, and whether the test chosen is consistent with a participants' preferences about the informational tradeoffs of adding moderate penetrance genes to a panel. Methods: An online hypothetical vignette study was completed by 454 people from the National Institutes of Health healthy volunteers database. Each participant was randomized to receive one of two survey versions which differed between a parallel or sequential presentation of testing options and the timing of the provider recommendation. Regression analyses were performed to determine the relationships between the choice presentation and participants' test decisions. Wilcoxon rank-sign tests were used to determine the impact of a provider recommendation on final genetic testing choices. Results: Participants were more likely to choose to undergo genetic testing when presented with three options instead of two (OR: 2.00 p=0.014). This effect was no longer observed when individuals who had decided not to undergo testing were presented with a third option (OR: 0.90 p=0.775). The addition of a provider recommendation did not significantly change the options chosen at a group level (p=0.746). However, individual participants were more likely to choose the test most consistent with informational preferences after a personalized recommendation (p<0.001). Conclusions: Participants are more likely to undergo genetic testing when presented with more options. They are also more likely to select an option in line with their own informational preferences following a clinician recommendation based on this preference.

Characterizing Personal Utility: A Systematic Literature Review

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1. Johns Hopkins University/National Human Genome Research Institute, National Institutes of Health

With the advancement of sequencing technologies that are faster and more cost-effective, the landscape of genomic medicine has shifted from a diagnostic to a preventive testing paradigm. One result of this shift is

that researchers and clinicians have recognized patient benefits of genomic testing results that are distinct from accepted clinical benefits. Non-clinical benefits have been termed "personal utility." Evidence of anticipated and experienced non-clinical benefits has been described in the literature inconsistently. Clearer understanding of the concept of personal utility will be important to evaluating the overall benefits of genome sequencing. The purpose of this study was to systematically review the literature to elucidate specific outcomes of genomic testing that comprise personal utility. An initial search returned 332 abstracts: 49 papers were read in full and 11 studies met the predetermined inclusion/exclusion criteria. Studies were both quantitative and qualitative in design conducted on various types of genomic testing from single-gene disorders to whole exome/whole genome sequencing for rare or complex disease. Meta-analysis of the study outcomes identified eighteen distinct concepts that fall into four domains: affective wellbeing, cognitive understanding, practical application, and social effects. Three domains were comprised of five concepts and the practical domain contained three concepts. Results from this review reveal a broader scope of patient-reported non-clinical outcomes. Each concept was reported in an average of three of the eleven studies (mean: 2.78, mode: 6). The concepts expand on previously reported outcomes of genetic testing, to include spiritual wellbeing and change in identity, among others. In a future study, the 18 concepts will be used to inform a Delphi study of participants in genome sequencing research to generate consensus data on the scope of personal utility. The ultimate goal of these efforts is to generate a comprehensive definition of personal utility.

Variant Sign-out Practices for Exome and Genome Sequencing Results: Current Roles of Genetic Counselors

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1. University of Washington
2. University of North Carolina at Chapel Hill
3. Illumina
4. Partners Laboratory for Molecular Medicine
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The nature of diagnostic exome and genome sequencing necessitates significant post-test variant interpretation to determine which variants, if any, meet the threshold for disclosure. This process of variant interpretation, sign-out and subsequent reporting has resulted in new and evolving genetic counselor roles. This work summarizes survey responses on variant sign out practices for exome and genome sequencing tests at nine CLIA certified research laboratories and ten clinical laboratories. At 4/10 clinical and 4/9 research laboratories, genetic counselors perform the primary analysis of bioinformatically filtered variants to identify an etiology of disease. Similarly, genetic counselors at both clinical (6/10) and research (3/9) laboratories perform the initial evidence gathering and review of individual variants. All 19 clinical and research laboratories include genetic counselors in multidisciplinary committees to discuss variants being considered for return. Genetic counselors are also involved in the development of the test report. In general, more clinical laboratories (7/10) than research laboratories (2/9) have genetic counselors write the initial draft of the report; however, this difference is only marginally significant (Fishers test p=0.07). When there is a second review of a case prior to sign out, genetic counselors are involved in reviewing and editing the report at both clinical (4/5) and research laboratories (2/4). The roles of genetic counselors in the process of variant sign out of exome and genome sequencing tests vary depending on the laboratory. The integration of genetic counselors throughout the genomic variant sign-out processes suggests that laboratories value the input of counselors in these efforts. With the continued growth of clinical and research applications of genomic sequencing, there is a need and opportunity to prepare genetic counselors to take on various roles in this process.

Estimating the Impact of Proposed FDA Regulation of Laboratory Developed Tests

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In 2014, the U.S. Food and Drug Administration (FDA) issued a draft guidance outlining a framework for the oversight of laboratory-developed tests (LDTs), a policy which could have a significant impact on patients seeking genetic tests and the providers who support them. The guidance outlines a risk-based framework for regulation, prioritizing the regulation of "high-risk" LDT's tied to medical actionability. It remains to be determined which tests fall into this "high-risk" category, and how numerous these products are. It is also unclear which tests will qualify for a rare disease exemption with a proposed cutoff of < 4,000 orders per test per year. Drawing from a database of more than 38,000 genetic testing products marketed by *Clinical Laboratory Improvement Amendments (*CLIA) certified U.S. laboratories, we set out to describe the industry-wide effects by determining the number of labs and tests affected by these proposed regulations. We defined high risk (Class III) as any test including a gene from the American College of Medical Genetics and Genomics list of 56 genes associated with high penetrance, preventable conditions (as a proxy for actionability) and any test tied to a specific drug or chemotherapeutic agent. Our analysis determined that there are 3115 different genetic tests available for clinical use that fall into this category, most of which would be considered LDTs. These tests are represented across 380 categories of tests and offered by 142 different CLIA-certified laboratories. Laboratory estimates for a Class III test to be taken through the FDA approval process are on the order of 1 million dollars per test. The remaining 35,533 tests would either fall into Class I or Class II depending on how low risk tests are defined, and how the rare disease exemption is applied. Laboratories would likely be required to submit a Premarket Notification 510 (k) before marketing a Class II test. Questions remain as to how the costs of regulation will impact the large and rapidly growing genetic testing market and ultimately patient access to testing. It is critical that policies be developed to fit the scope and expanding, evolving nature of the genetic testing marketplace.

The Importance of Carrier Screening in Individuals of Sephardic, Mizrahi, and Persian Jewish Descent

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Background: In the United States, professional society guidelines for Jewish carrier screening center on those of Ashkenazi Jewish ancestry. However, people of Sephardic, Mizrahi, and Persian Jewish descent are at increased risk for certain disorders as well. Very few laboratories offer a Sephardic/Mizrahi/Persian Jewish carrier screening panel and there are no published medical guidelines for carrier screening in patients of Sephardic/Mizrahi/Persian Jewish ancestry. Methods: Community-based screening events were held at multiple sites between January 2014 and February 2015. Participants who self-identified as having at least ¼ Sephardic, Mizrahi, or Persian Jewish ancestry were offered a panel of eight DNA based carrier screening tests and a hemoglobinopathy evaluation. All participants were provided pre-test information by a genetic counselor and informed consent was obtained prior to blood draw. Positive test results were called to patients by a genetic counselor. Results: Three hundred five patients underwent carrier screening and 88 individuals

(28.9 %) tested positive for at least one disorder. Five individuals tested positive for more than one condition. Sixteen participants were identified as affected with glucose-6-phosphate dehydrogenase (G6PD) deficiency (15 males and 1 female). The most common conditions detected were G6PD (27 carriers, 8.9 %: 16 affected 5.2 %), familial Mediterranean fever (19 carriers, 6.2 %), and hereditary inclusion body myopathy type 1 (17 carriers, 5.6 %). Conclusions: Jewish individuals of non-Ashkenazi ancestry are at risk for certain disorders, but clear screening guidelines do not exist. As a result, access to testing may be more limited compared to those of Ashkenazi Jewish descent. This small data set demonstrated that about 1 in 4 individuals of Sephardi/Mizrahi/Persian Jewish ancestry are positive for at least one condition on this panel. Further research is needed to evaluate the most effective screening panel for this population.

Updates from the Canadian Open Genetics Repository (COGR): A Unified Clinical Genome Database as a Community Resource for Standardizing and Sharing Genetic Interpretations

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The arrival of the genomics era has increased the quantity and complexity of data produced by genetic laboratories. Initially, labs anticipated there were a finite number of variants and increased adoption of sequencing would lead to a declining number of novel and uncertain variants. This has not been the trend thus far, prompting the critical need for data sharing efforts. The Canadian Open Genetics Repository (COGR) is a collaborative effort for the collection, sharing and analysis of variants reported by diagnostic laboratories in Canada that can serve as a focal point for other international data sharing efforts. The goals of the project are three-fold. First, facilitate standardization of the assessment process via a freely available Variant Assessment Tool (VAT). Second, each COGR lab receives a free instance of GeneInsight®, a database featuring versioning of variant assessments and interpretations, plus functionality to enable real-time sharing of this information between labs. Finally, curated variant data will be presented to various stakeholder groups in appropriately understandable formats and levels of summary. Here we present an update to this initiative. To date, 20 institutions have a GeneInsight instance, six are sharing variant data including over 6,000 intragenic and copy number variants. Focus has now shifted to the last aim. The COGR members are now identifying variant discrepancies through anonymous discrepancy reports. Variants are proposed to reach consensus level if three or more labs agree on an interpretation. Currently 37 variants match this criterion. In cases where the reports are not sufficient to create concordance, a majority vote will be sufficient to reach 'majority level' agreement. These consensus and majority level variant interpretations will then be displayed on a publicly accessible site. As a continuing effort, the COGR endeavors to increase genetic knowledge and standardization through data sharing and consensus building, ultimately improving our ability to diagnoses and treat genetic diseases.

IV. Professional Issues and Education

Transition Curriculum: An Educational Framework for Supporting Genetic Counseling Students

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Genetic counseling students face the educational challenge of transitioning from entry-level graduate students to practicing certified genetic counselors in 2–3 years. Often students are also transitioning from an undergraduate educational model to a professional graduate school setting. Transition programs are well established both in educational and clinical settings and have been shown to improve educational and health outcomes. However, they have yet to be applied to genetic counseling education. We describe an educational framework to support genetic counseling students' professional development during their transition to practicing genetic counselors. Learning outcomes of this curricular framework focus on professional development in four main areas designed to reflect the four domains of the Accreditation Council for Genetic Counseling (ACGC) Practice Based Competencies. This framework is structured to support students' transition (I) from rote memorization to independent clinical application of material; (II) to gradually increase student independence and responsibility as a member of a clinical and educational team; (III) to develop the educational skills required for clinical and supervisory practice; and (IV) to establish self-reflective practice as a foundation for professional development. Educational activities based on this framework are described, including: transparency of educational design; near-peer mentoring; clinical supervision role-play; regular reflective writing practice; and discussion and self-evaluation of the ACGC practice-based competencies. While many genetic counseling programs have included similar educational activities as part of their educational structure, there is little published on the educational theory and tools utilized in these activities. This educational framework and related educational activities are described with the goal of demonstrating the application of the educational theory of transition to the professional development of genetic counseling students.

Students' Perceptions of Supervision Across a Year of Clinical Rotations

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As increased focus is being paid to supervision of genetic counseling students, it is vital to examine student perceptions of the process in addition to those of supervisors and educators. While the body of empirical literature about student supervisees is growing, no research to date has followed students longitudinally throughout their clinical rotations to determine if and how their perceptions shift as they gain experience. To that end, the current study sought to examine students' perspectives on supervision near the beginning and end of clinical training. Phone interviews with a national sample of 40 genetic counseling students beginning their second year and follow-up interviews with 32 of these students at the end of their second year were transcribed and analyzed using consensual qualitative research methods. As students gained more experience, the focus of their comments on supervision shifted from focusing on content and evaluation (e.g., receiving feedback, clarifying expectations, managing feedback from multiple supervisors) to emphasizing process and relationship aspects (e.g., connection, trust). For example, during the first interviews, students highlighted the importance of type and frequency of feedback from supervisors as the most important aspects of supervision. During the second interviews, however, the support and encouragement provided by supervisors was highlighted as most important. Additionally, the quality of supervision interactions became more powerful influences on students' perceptions of their rotations as they gained more experience, and students expressed less anxiety regarding supervision and their clinical work in general. Training programs can leverage these findings to help students understand their development and prepare for upcoming challenges. Supervisors can also use the findings to better prepare for

students' expectations. Further research should investigate what factors moderate this relationship and explore the relationship between supervision perceptions and actual performance.

A Sustainable Model for Blended Learning in Genetics and Genomics

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Despite a recognized need in the medical community for improved integration of genetics into practice, significant barriers limit widespread implementation. Key to successful implementation is a genetically educated and aware workforce. We describe a novel approach to genetics education for the non-geneticist clinician that uses best practices in adult education, is highly interactive and clinically relevant, and utilizes the benefits of both in-person and digital delivery for maximum educational impact. The Jackson Laboratory and the American Society of Human Genetics developed and implemented an interactive educational program to improve the clinical skills of primary care providers (PCPs) in assessing and managing genetic risk for cancer. This blended learning program consists of online pre-work, 6.5 hours of in-person content, monthly communications, and access to digital resources. The approach to in-person curriculum emphasizes skill-building by modeling a patient interaction followed by immersing the participants in practice cases with immediate expert feedback. The program includes presentation slides with professional graphics and supporting key messages and notes, facilitator guides, and handouts (factsheets and tools) as well as reusable digital educational activities. The program was initially piloted with 21 PCPs in 2014. Participants demonstrated significantly improved confidence, attitudes, and knowledge related to genomic risk assessment. These early results suggest that this innovative program can build PCP skills in the assessment and management of hereditary cancer, supporting improved patient care. This model of blended learning is easily reusable and sustainable to implement again after the initial development is complete. Based on this successful pilot, the program will be implemented broadly and will serve as a framework for future programs and expanded audiences to improve clinical integration of genetics into practice.

Interpreting for Genetic Counselors: Identifying Common Pitfalls and Solutions

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In 2011, approximately 25.3 million individuals in the United States had limited eEnglish proficiency. Communication issues due to language and cultural diversity can significantly impact healthcare quality. To overcome these obstacles, medical interpreters are used to facilitate communication between providers and patients. The goal of this study is to identify challenges interpreters face during genetic counseling sessions and provide insight in how genetic counselors and interpreters can effectively collaborate to improve communication with patients. The study targeted certified medical interpreters working at several hospitals in Chicago to participate through an e-mail invitation distributed by their managers. Participants were interviewed over the phone using a semi-structured interview guide. Interviews were audio-recorded and transcribed verbatim. Coding rules were established via exhaustive coding. A joint codebook was developed and assessed for inter-rater agreement (κ = .85). All codes were reviewed for modification/relabeling. Following open coding of the data, axial coding ensued, which consisted of identifying relationships among concepts and categories. Fourteen in-house medical interpreters discussed the process of interpreting, factors that affect genetic counseling sessions, challenges that arise during sessions, and provided feedback for genetic counselors. Challenges described included the difficulty accessing genetic counseling materials, terminology used, and the complexity of the information discussed. Interpreters recommended meeting for a pre- and post-session when possible and reported the need for a reference that covers genetic counseling terminology and common phrases to promote their proficiency. Participants voiced a desire for an online tool that reviews basic genetics concepts to enhance their overall understanding of the information discussed. Genetic counselors could collaborate with interpreters in the creation of a reference aid and an online tool in order to increase interpreter's familiarity with the genetic counseling field.

Design, Implementation, and Outcomes of a Psychiatric Genetics for Genetic Counselors (PG4GC) Workshop in the UK

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Knowledge about the roles of genetic and environmental contributors to the development of psychiatric disorders is accumulating rapidly, and concurrently, the importance and urgency of translating this knowledge into better health is increasing. The first specialist psychiatric genetic counseling (PGC) service of its kind opened in Vancouver in 2012, generating interest from healthcare professionals from around the world who wish to develop similar services. In responding to this interest, we noticed that for many of these individuals, the barriers to their provision of high quality specialist services for individuals with psychiatric disorders and their families related to four core issues: lack of familiarity with specialist (psychiatric and/or genetic) terminology, feeling out of touch with the state of the art in psychiatric genetics, lack of confidence in discussing psychiatric disorders – both in general, and their etiology (in lay language) specifically, and uncertainty regarding how to discuss the risks for illness recurrence amongst family members of affected individuals. Therefore, with a target audience of genetic counselors in mind, we developed an intensive 2-day workshop (PG4GC) that aimed to address these four core issues and form the foundation for the development of a strategy for delivering PGC both within the United Kingdom (UK) and globally. The workshop, which was delivered in the UK in Feb 2015, incorporated didactic content, small and large group discussion, a problem based learning case, and individual reflective work. In total, 23 participants from seven countries attended and completed pre- and post-workshop surveys, which revealed that participants were more confident with respect to all four core issues after the workshop. At the conclusion of the workshop, participants founded the International Society for Psychiatric Genetic Counseling (ISPGC, which interested counselors are welcome to join). Members of this fledgling organization will meet at the 2015 World Congress of Psychiatric Genetics, and plans are underway for a second PG4GC workshop in 2016.

Development of EMPOWER: Evaluation Model for Patient Outcomes When Engaging in Reciprocal Communication as Part of Genetic Service Delivery

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As healthcare reimbursement is progressively tied to value-of-service, it is critical for the genetic counseling profession to systematically and quantitatively demonstrate the value added by genetic counselors (GCs) through outcomes research. To advance future research, a comprehensive approach is needed to organize the broad array of potential outcomes and to postulate relationships between genetic service delivery (GSD) processes and outcomes. Methods: Through an iterative approach involving literature review, thematic analysis, and consolidation, we categorized GSD outcomes, processes, and strategies to create and define components of a model and generate an illustrative example. Results: The resulting model is termed EMPOWER: "Evaluation Model of Patient Outcomes When Engaging in Reciprocal Communication" and consists of multiple constructs organized within the following seven domains: patient and provider goals; GSD strategies; process constructs, stakeholder constructs, service system outcomes; patient outcomes (proximal, intermediate, health); and family outcomes. The utility and flexibility of the model is illustrated through postulating mechanisms whereby GSD may influence outcomes. For example, process constructs hypothesized to influence family communication may include "eliciting communication facilitators and barriers" and "providing informational resources for patients to share with family." Proximal patient outcomes may include, "patient is empowered to use resources to communicate with family." Family outcomes could include, "genetic information is communicated to family members" and "appropriate uptake of genetic services by family members." Conclusion: This is the first conceptual framework that comprehensively defines a broad array of GC process and outcome constructs and postulates general relationships between framework domains. Using this type of theoretical model could provide a valuable resource that will address three NSGC strategic objectives and be used to align quality measures and promote necessary GC outcomes research and evidence-based practice.

V. Access and Service Delivery II

The Beneficial Role of the Laboratory Genetic Counselor in Test Utilization Management: Evidence and Opportunities from a Multisite Study of Provider Satisfaction

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Seattle Children's Hospital (SCH) and Lurie Children's (LC) employ laboratory genetic counselors (GCs) in active utilization management (UM) programs to improve the value of laboratory tests for patients. These programs are driven by similar goals of reducing incorrect or unnecessary tests and avoiding excess financial liability for patients, families and institutions. Approximately 50 % of PLUGS (Pediatric Utilization Guidance Services) member institutions list provider culture as one of the biggest challenges to implementing case review. To validate the benefits of engaging laboratory GCs in UM case review, provider satisfaction surveys were conducted at our respective institutions. The 10-question survey was designed to capture the provider's perspective using a semi-quantitative scale where 50 % is a neutral response. At SCH, 216 providers were surveyed in 2013 and 182 providers in 2014, with a 46 % and 40 % response rate, respectively. At LC, 305 providers were surveyed in 2014, with a 22 % response rate. A comparison of data between SCH and LC showed strikingly similar responses across the questions, with providers appreciating the support of the UM programs and the support of a laboratory genetic counselor in particular. The highest median satisfaction (82 % at SCH and 88 % at LC) was related to the question, "I appreciate knowing that the laboratory UM program supports me and my patients (e.g. catching instances of duplicate orders, helping me stop unnecessary patient-driven testing, etc.)." The lowest median satisfaction (50 % at SCH and 52 % at LC) was related to questions regarding preauthorization support and processes. The results affirm each program's approach to case review and highlight the positive effect of the genetic counselor in the UM process. The results also identified opportunities for improvements. To that end, both SCH and LC have proposed algorithms leveraging the laboratory GC to promote standard, efficient genetic testing preauthorization coordination through the UM program and institutional preauthorization teams.

Demonstrating Feasibility of a Collaborative Approach to Cancer Risk Assessment Services in a Multi-System Community Hospital

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Most board certified genetic counselors (CGCs) in Indiana who specialize in cancer genetics are based in large cities. To provide improved access by smaller rural communities, the St. Vincent Hospital Cancer Genetics Risk Assessment Program designed a unique approach to cancer risk assessment. This study reports on the experience with one collaborating hospital over a 2-year period. Local, on-site nurse navigators received training from the CGCs, including observation of genetic counseling sessions and on-line courses. From August 2012-July 2014, 12,477 patient family history questionnaires representing 8,937 unique patients having a screening mammogram or new oncology appointment at the remote site were triaged by CGCs. Of these, 8.2 % patients were identified at increased risk for hereditary breast cancer with the offer to meet with a nurse navigator for further risk assessment and potential *BRCA1/2* testing, while 4.2 % were identified at increased risk for other hereditary causes of cancer with an offer for evaluation with a CGC during a monthly outreach clinic. A total of 171 patients reponded to a notification letter, resulting in 23 patient visits with the nurse navigator and 52 patient visits with a CGC. An additional 30 patients were seen on-site by a CGC as a result of referals from local physicians aware of the service, for a total of 105 patients. When coordinated by the nurse navigator, results of all genetic testing were reviewed by a CGC to determine the need for additional testing and risk interpretation. Efficiency of this model was assessed by determining time spent by the CGC in all activities related to the collaboration, which amounted to approximately 16 hours per month. This study demonstrates the feasibility of collaborating with trained and supported genetic counselor "extenders" to improve access to and efficiency of a CGC without sacrificing quality or becoming overburdened.

Increasing Genetic Counseling Referrals for Women with Ovarian Cancer: Utilization of a Best Practice Advisory in the Electronic Medical Record

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Introduction: Genetic counseling is recommended for all women with epithelial ovarian, fallopian tube, or primary peritoneal cancer. However, many studies have shown that the majority of these patients are not referred to genetics. As targeted therapies emerge for women with ovarian cancer due to mutations in *BRCA1/2,* genetic counseling and testing are increasingly vital. Methods: We developed a Best Practice Advisory (BPA) within the Electronic Medical Record (EMR) to prompt clinicians to discuss genetic counseling with patients. The BPA was triggered for healthcare providers in gynecologic oncology during a patient encounter in the presence of ICD-9 codes for ovarian, fallopian tube, and primary peritoneal cancer. Choices to acknowledge the alert were: order a consult

to genetics, indicate testing was already performed, defer, or decline due to patient choice. Results: Over 17 months, the BPA triggered for 328 patients with high grade epithelial cancer who had not had genetic counseling or testing in the past. 192/328 (59 %) were referred for genetic counseling. Of those patients, 135/192 (70 %) had genetic counseling, and 129/135 (96 %) elected genetic testing. A deleterious mutation(s) was identified in 27/129 (21 %) (12 *BRCA1*, 9 *BRCA2*, 3 *BRIP1*, 1 *ATM*, 1 *TP53*, and 1 *BRIP1* and *BARD1*). Compared to the pre-implementation period (1/2011-10/2013), significantly more patients were referred for genetic counseling after implementing the BPA (192/328 (59 %) vs. 158/365 (43 %) $p<0.0001$). Limitations: Programming errors caused the BPA to trigger inappropriately, causing user frustration. Conclusions: Use of a BPA in the EMR for women with ovarian, fallopian tube, and peritoneal cancers significantly increases genetic counseling referrals and identification of important mutations in a high percentage of patients that could alter medical management. Edits to the program may help decrease rates of misfiring and make the advisory less intrusive to clinicians while affording women the opportunity to pursue genetic testing.

Retesting Patients with Multi-Gene Hereditary Cancer Panels: The Impact on a Genetic Counselors' Patient Volume

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The existence of hereditary cancer gene panels has led to providers pinpointing which former patients should be offered reflex genetic testing for Hereditary Breast and Ovarian Cancer (HBOC) syndrome. Part of this equation includes being aware of the effect this will have on clinic volume. To address this, we reviewed the histories of 9,854 patients to determine a priori BRCAPro (ABP) risks, triple negative (TN) status, and ovarian cancer (OC) diagnoses, as these patients have been deemed as high-risk patients for finding a non-BRCA mutation. We analyzed different ABP cutoffs for retesting and found an ABP >90 % results in a 2.42 % increase in patient volume; >60 % ABP = 3.26 %; >40 % ABP = 5.47 %; >20 % ABP = 8.29 %; >10 % ABP = 11.71 %. These numbers were similar between both the private (73.52 %) and underinsured (26.48 %) clinic populations. 2.70 % of all patients would need re-testing due to their diagnosis of TN breast cancer; 2.67 % of all patients with OC would need re-testing. Although these three categories are not necessarily independent of one another, these data help estimate the impact of re-testing BRCA negative patients. A clinic of 300 patients annually would experience a 13.66 % (41 patients) increase in clinic volume using the criteria of >20 % ABP, TN breast cancer, and OC patients; the same clinic would experience a 16.77 % (51 patients) increase if the criteria were >10 % ABP, TN breast cancer, and OC patients. Genetic counselors need to be aware of the impact re-testing will have on their clinic volume, be prepared to prioritize the highest risk patients for re-testing, and educate their referral sources about appropriate patients for re-testing.

Decision-Making Across Cultures: Cancer Counseling of Low-Income Latina Women Using Medical Interpreters

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In cancer genetic counseling (CGC), a model of practice based on shared decision-making (SDM) challenges communication with limited English proficiency (LEP) patients, exacerbating existing health disparities. Limited research has examined the decision-making process of low-income LEP patients in CGC. This study investigated the extent to which communication was effective with low-income LEP Latina women in CGC, how this communication affected decision-making, and identified potential strategies leading to improve effective communication and SDM with this population. We analyzed audio recordings, drawn from a larger study, of CGC sessions with low-income LEP Latina women conducted with professional medical interpreters via telephone in two public hospitals. Audio files were coded directly by two bilingual english-spanish speakers and analyzed using conventional content analysis through an iterative process. Twenty-four CGC sessions involving 13 patients and 6 genetic counselors were included. We identified two domains that inhibited effective communication and SDM: the use of hypothetical scenarios and misinterpretation by the medical interpreter. A third domain, communication facilitators, involved strengths that enhanced effective communication and SDM. Overall, there was an absence of patient participation in the decision-making process. Our data suggest that when counseling across language and culture via medical interpreter, genetic counselors should present information in a way that clearly demonstrates its utility for the patient, for example by explaining or modeling how to integrate the information presented into the decision-making process. Genetic counselors should also consider organizing information into short-term and long-term goals to increase its utility, lessen information overload, and improve comprehension for patient and interpreter. Further research is needed to understand how applicable our findings are to other populations.

Comparing Knowledge Gain Between in-Person and Telemedicine Genetic Counseling for Hereditary Breast Cancer

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The demand for genetic counseling services for hereditary breast and ovarian cancer has been rapidly increasing. In order to provide wider access to these services across large geographic areas, the use of telemedicine has been expanding. Little is known, however, about the effectiveness of telemedicine in increasing patients' knowledge of cancer genetics. Our study aimed to compare knowledge gain between in-person and telemedicine genetic counseling sessions for hereditary breast cancer risk. Using a seven item questionnaire adapted from previous studies, participants' knowledge of hereditary breast cancer was assessed immediately prior to and immediately following counseling sessions at an in-person cancer genetics clinic and three telemedicine sites. We hypothesized that there would be significant knowledge gain for both in-person and telemedicine groups and there would be no differences in final knowledge between the two groups. There were 162 participants who received in-person genetic counseling and 77 participants who received telemedicine services. Knowledge level was measured by number of correct responses; a general linear model was used to compare groups and control for patient education level. Knowledge post-counseling did not differ significantly by genetic counselor. For both groups, the number of correct responses on the questionnaire was significantly higher after counseling, $F(1, 233) = 171.95$, $p < .0001$. While there were no significant differences in participants' pre-counseling knowledge between in-person and telemedicine groups, individuals who received counseling via telemedicine had significantly fewer correct responses than those who received in-person counseling when controlling for education level, $F(1, 233) = 3.87$, $p = .049$. With genetic counseling services continuing to expand using alternate models of care, it is important to ensure that patients receive adequate knowledge for decision making regarding genetic testing across all service delivery models.

VI. Clinical Care: Counseling and Psychosocial Perspectives

Roles for Religion and Spirituality in Genetic Counseling

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Religion and spirituality (R/S) can inform healthcare decisions and support patients when faced with medical issues. While a majority of genetic counselors (GCs) believe that R/S should be addressed during a session, they rarely or never inquire about patients' R/S practices. This study explored barriers GCs face performing a R/S assessment. A focus group guide developed by the research team based on a literature review explored participants' definitions of R/S, perceived value(s) in clinical care and roles for non-spiritual care providers in R/S discussions. Following an initial piloting with GC students, a focus group was held with six GCs in a major medical center. Participants had an average of 8y GC experience (1–18 y) and represented cancer, prenatal, pediatric and ophthalmologic genetic specialties. Two independent reviewers used an iterative coding process based on content analysis and grounded theory to identify 26 codes (utilized 438 times) that coalesced into 5 themes. We found that GCs are 1) generally passive when addressing R/S topics, relying on patients to lead the discussion; 2) uncertain regarding how to perform a R/S assessment, their responsibility, and relevance to the session; 3) reluctant to engage in R/S discussions due to fears including offending patients or disclosing one's own R/S practices; 4) concerned that R/S inquiry could interfere with the genetic counseling process (e.g. patient's attributing conditions to "God's will" may impact education and decision-making); and 5) have limited knowledge and experience with services provided by chaplains. Participants expressed a willingness to partner with clergy to learn about R/S assessments and support. While GCs recognize R/S assessment as potentially relevant in some instances, utilization is hampered by limited knowledge, discomfort in crossing boundaries and fears that R/S affects the GC process. Our results highlight the complex barriers that limit a GC's R/S assessments and opportunities for partnerships with chaplains as a means of enriching patient care.

Spiritual Exploration in the Prenatal Genetic Counseling Session

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Religion and spirituality (R/S) are important components of many individuals' lives, and spirituality is often employed by women coping with pregnancy complications. To characterize how prenatal genetic counselors might address spiritual issues with patients, 283 English and Spanish speaking women receiving prenatal genetic counseling in Houston, Texas were surveyed post-counseling using both the Brief RCope and questions regarding interest in spiritual exploration. Counselors were concurrently surveyed to identify religious/spiritual language used within sessions and perceived importance of religion/spirituality. Counselors were significantly more likely to identify R/S as important to a patient when patients used religious/spiritual language ($p<0.001$). Conversely, when no religious/spiritual terms were present, the counselor felt uncertain about the importance of R/S 63 % of the time. Significant associations were found between patient desire to talk about faith in the session and the use of the terms God, believe/belief, Christian, church, faith, God's hands, God's will, pray, and religion ($p<0.05$). Overall, 67 % of patients reported that they felt comfortable sharing their faith as it relates to pregnancy, and 93 % reported using positive religious coping. Less than 25 % reported a desire for overt religious actions such as prayer or scripture exploration. Patients who desired overt religious actions had significantly higher levels of positive religious coping ($p<0.05$) and negative religious coping ($p<0.05$) and may benefit from a referral to pastoral services. However, the majority of patients' desires for spiritual exploration centered around the decision making and coping processes that are in line with the genetic counseling scope of practice. Therefore, counselors should feel empowered to incorporate spiritual exploration into their patient conversations. Genetic counselors may consider adding a question about the impact of R/S in pregnancy on intake forms and/or inquiring about R/S while taking a pedigree to inform the desire for exploration of this topic.

Peering Down the Rabbit Hole: Living with von Hippel-Lindau Syndrome from the Young Adult Perspective

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Von Hippel-Lindau (VHL) is a hereditary cancer susceptibility syndrome that requires rigorous lifelong surveillance. Annual screening is age-based, involving retinal exams after the first year of life and imaging of the brain, spine and abdomen starting in adolescence. Surgical or other interventions may become necessary to prevent secondary effects such as vision loss or cancer metastasis. Given the young age at which symptoms manifest, many patients undergo multiple screening and treatment procedures by adulthood. Few studies have described the psychosocial aspects of living with VHL and have not addressed issues specific to emerging young adults. Accordingly, we conducted a qualitative study to explore the experiences of ten young adults (18–26 years old) with VHL residing in the United States. We recruited participants through the VHL Alliance and administered semi-structured telephone interviews that addressed five major topics: personal and familial experiences with VHL, support systems, emotional well-being, effect of VHL on romantic and familial relationships, and effect on life decisions. Thematic analysis of the interview transcripts was performed in ATLAS.ti (v.7.5.4) and five themes emerged: (1) living with uncertainty, (2) maintaining a positive attitude, (3) family members as significant means of support, (4) polarizing effect on relationships, and (5) impact on life decisions with respect to location, career path, and childbearing. We conclude that living with VHL as a young adult involves a considerable psychosocial component that extends beyond the well-studied physical aspects of the syndrome. Young adults with VHL would likely benefit from establishing a long-term relationship with a genetic counselor, as they can help manage uncertainty, connect patients with other young adults living with VHL, and provide education regarding childbearing options. Further research with this population will likely help genetic counselors and other health professionals provide better support and services to young adults living with VHL.

Development and Use of a Novel Scale: Parents' Uncertainties About Their child's Health

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Uncertainty pervades all aspects of medicine and is specifically relevant to those affected with rare and undiagnosed conditions. Research has demonstrated that uncertainty can be a significant source of psychological distress and of key importance in genetic counseling. The aim of the current study was to assess the reliability and validity of a novel scale designed to assess perceptions of uncertainty. Validated scales were used to assess coping efficacy, tolerance for uncertainty, dispositional optimism and resilience. Open-ended questions were used to explore responses to uncertainty. Ninety-four parents of children with undiagnosed medical conditions, recruited from online advocacy groups, completed the survey. Respondents were predominantly biologic mothers and averaged 38.6 years old. The mean age of the children was 8.0 years and most were female (57 %). The Parents' Uncertainties about their Child's Health Scale (PUCHS) was designed to include seven domains of uncertainty. Each domain was measured using two items that assessed the specific source of uncertainty followed by two parallel questions about the perceived importance of each item. The items for the scale originated from the literature and our past studies. To capture parental priorities, each item was weighted by importance. Exploratory factor analysis indicated convergence into five factors: Medical (α=0.84), Future, Reproductive (0.62), Social (0.81), and Existential (0.94). The Future factor consisted of one item and was dropped from the scale, resulting in four final domains. The greatest variance in the PUCHS was accounted for by Medical uncertainty. Initial evidence for discriminant validity data was established by correlations of the PUCHS with measures of dispositional optimism and resilience, such that individuals with higher dispositional optimism and resilience tended to have lower levels of weighted uncertainty. These results provide preliminary evidence to support the use of this scale in future studies of parental coping and adaptation to having a child with an undiagnosed disease.

Psychological Impact of Exercise Restrictions in Recreational Athletes with Hypertrophic Cardiomyopathy

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Individuals with hereditary cardiovascular conditions, like hypertrophic cardiomyopathy (HCM), are recommended to restrict their athletic activities in order to reduce their risk of sudden cardiac death. Clinical experience and prior studies suggest that these restrictions can be a source of psychological distress for some individuals; however, this has not been specifically studied. We used semi-structured telephone interviews to explore the psychological effect of exercise restrictions on athletes with HCM and the adaptive and maladaptive techniques used to adjust to the restrictions. To obtain a rich sample, we performed purposive selection of self-identified recreational athletes who had difficulty adjusting to their exercise restrictions. Sixteen (9 men, 7 women) individuals participated, with a mean age of 52. Data was analyzed using a modified grounded-theory approach, which included thematic coding. The majority of individuals could not identify positive effects from their restriction, but could report various long-term negative effects including weight gain and feelings of uncertainty surrounding exercising safely. Participants experienced a shrinking of the role of exercise from a myriad of functions (social, stress relief, fitness) to solely health maintenance. The majority expressed a desire for more concrete and individualized exercise recommendations. Adaptive coping strategies included getting educated; communication with support network surrounding restrictions; and having family and friends participate with them in lower intensity exercise. Lack of understanding from family or friends about the emotional difficulty associated with reducing athletic involvement was hurtful. Many reported that avoiding exercise completely was detrimental. These findings suggest that clinicians can help athlete's adapt to exercise restrictions by using an individualized approach that includes discussing the emotional impact, addressing methods to fill the void of exercise, creating a specific exercise plan and helping the patient activate their support network.

Knowledge and Self-Esteem of Individuals with Neurofibromatosis Type 1

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Neurofibromatosis Type 1 (NF1) is a progressive genetic disorder characterized by café-au-lait macules, Lisch nodules, as well as neurofibromas among other traits. Learning and social problems are also more prevalent in this population. Due to the visible and nonvisible manifestations of the condition, it has been observed that individuals with NF1 have lower self-esteem (SE) when compared to the general population. Additionally, a study published over 20 years ago found that overall knowledge of NF1 was poor in individuals affected with the condition. The goal of our study was to reassess knowledge in this population and investigate whether it is related to SE. Furthermore, we explored the impact of other factors on knowledge and SE. A survey comprised of knowledge-based questions and the Rosenberg Self-Esteem Scale was distributed to individuals with NF1 through the Texas NF Foundation. Overall, the 49 respondents (13 to 73 years old) had higher than expected knowledge of NF1 (mean score = 77.9 % correct answers) across various aspects of the condition. Consistent with previous studies, the SE of our study population was lower when compared to general population norms. Although no correlation between knowledge and SE was observed, SE scores were on average higher if a person reported to have friends with NF1 (p=0.009), attended an NF1 support group (p=0.006), attended an NF clinic (p=0.049), or received genetic counseling (p=0.008). Having friendships with people who have the same condition as well as attending support groups may help those affected by NF1 to feel less isolated and increase their SE. Additionally, genetic counseling provides an opportunity for these individuals to identify positive coping strategies such as educating peers about NF1 and therefore may help boost SE.

VII. Clinical Care: Pediatrics and Adults

Predispositional Genome Sequencing in Healthy Adults: First Findings from the PeopleSeq Study

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Introduction: Several clinical and research programs offer whole genome (WGS) or whole exome sequencing to ostensibly healthy adults, for education and prognostic purposes. Though such personal/predispositional genome sequencing (PGS) may prove to be a valuable tool for improving

health, the outcomes of providing PGS remain poorly documented. Purpose: As part of the Personal Genome Sequencing Outcomes (PeopleSeq) Study, we sought to understand participants' motivations for obtaining PGS, and their attitudes on sharing PGS results. Methods: We piloted our survey with participants from Illumina's Understand Your Genome (UYG) program, which offers WGS to ostensibly healthy, paying adults, and returns a clinically focused report to each participant via her/his ordering physician. Online, we uniformly surveyed 292 UYG participants about their motivations for PGS, perceived utility of their results, and attitudes on sharing results. We used descriptive statistics and chi-square tests to examine data from 70 (24 %) UYG individuals. Results: Reported motivations for seeking PGS included personal interest in genetics (100 %), and curiosity about their own genetic make-up (99 %). Respondents motivated by family history of a possible or confirmed genetic condition (31 %) were likelier than others to report learning something from PGS that they believed would improve their health (p=0.006). As a result of receiving their PGS results, 21 % of respondents made appointments with a medical professional, 11 % had a medical exam/procedure, and 4 % had a genetic test to confirm a variant in their PGS results. Respondents reported discussing their results with family members (87 %), co-workers/colleagues (80 %), friends (70 %), and healthcare practitioners (60 %). Conclusions: Survey respondents reported high genetic curiosity, and willingness to discuss their results with others. Respondents who sought PGS for family history concerns were likeliest to report receiving useful health insight. PGS results motivated many, though not all, respondents to obtain additional medical care.

ACMG Recommended Secondary Findings are Identified in only 2.25 % of Pediatric Patients Undergoing Exome Sequencing

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1. Ambry Genetics

Background: Diagnostic exome sequencing (DES) is a powerful diagnostic tool to provide a molecular diagnosis for patients with undiagnosed genetic disease and may result in identification of secondary findings (SF). Following the publication of American College of Medical Genetics and Genomics's (ACMG) "Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing," genetic counselors are integral to providing patients with clear expectations. Pre-test counseling is especially important for pediatric patients, as many of the genes on the ACMG list are adult onset conditions or cancer susceptibility syndromes. Methods: We performed a retrospective analysis of the SF results identified in the first 400 pediatric patients undergoing DES, electing ACMG minimum secondary findings gene results. SF reports were only offered for the proband and included part of the DES testing. Clinicians were re-contacted following a positive SF report to determine if additional family history of the condition had been obtained. Results: Overall, 9 (2.25 %) of the 400 patients were identified to carry a pathogenic mutation in one of the ACMG recommended genes. Of these reported mutations, 5 (55.6 %) were in cancer genes (2 - *BRCA2*, 1 - *BRCA1*, 1 - *APC*, 1 - *TP53*), 3 (33.3 %) in cardiac associated genes (*DSC2, KCNQ1, MYBPC3*), and 1 (11.1 %) a mutation causing susceptibility to malignant hypothermia (*RYR1*). A family history of cancer meeting the NCCN guidelines for testing an affected family member was not reported in 3 of the 5 positive cases (60 %). Additionally, individuals that tested positive for cardiac genes and malignant hypothermia did not have a reported family history consistent with the diagnosis. Conclusions: Despite initial concerns regarding reporting of ACMG secondary findings, the number of positive cases is low in pediatric patients. An important observation was that the majority of patients who tested positive did not have reported family histories of these conditions. These findings underscore the importance of pre and post-exome counseling in order to aid in the interpretation of SF results.

Research Participation in the Duchenne Muscular Dystrophy Community: Parent Perceived Barriers and Their Impact on Families

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Purpose: Duchenne Muscular Dystrophy (DMD) is a degenerative neuromuscular disorder causing severe progressive muscle loss and premature death. While research in DMD is critical to advance treatment and care it also presents many challenges for families, which can affect research recruitment. Poor recruitment constrains the ability to achieve and measure progress in clinical research, and consequently affects how well new therapies perform. The purpose of the present study was to identify barriers to research participation in DMD research and to explore how these barriers impact families. Methods: In collaboration with the Cooperative International Neuromuscular Research Group (CINRG) academic clinical research network and associated Muscular Dystrophy Association (MDA) clinics, parent-centered focus groups were conducted at five sites: Pittsburgh, PA; Washington, DC; Minneapolis, MN; Houston, TX; and Sacramento, CA. A total of eight guided focus groups attended by 28 parents of boys with DMD were audio-recorded and transcribed. Qualitative thematic analysis of focus group transcripts was conducted to identify themes. Results: Major themes identified as barriers to research participation included: 1) commitments; 2) fighting a new battle; and 3) the gamble. Participating in research was shown to affect many aspects of participants' lives and additionally had an impact on the entire family. Conclusions: Identifying barriers to research participation and understanding how these barriers impact families can provide information to improve research protocols and facilitate development of strategies to encourage greater research involvement. These findings highlight the need for greater support and appropriate resources to alleviate potential barriers faced by families. Genetic counselors are well suited to communicate research opportunities, address the specific needs of families, educate families on complex research issues, and explain study eligibility criteria due to mutation-specific approaches in many DMD research studies.

Sleep Disturbances in Children with Phelan-McDermid Syndrome and Their Caregivers

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1. Stanford University

Background: Phelan-McDermid syndrome (PMS) is a neurodevelopmental disorder caused by haploinsufficiency of the SHANK3 gene. Sleep problems in children with PMS are anecdotally common but not well characterized. Study objectives were: 1) to describe parent-reported sleep disturbances in children with PMS, 2) to investigate whether children with PMS are routinely assessed for sleep disorders, and 3) to examine the correlation between child and caregiver sleep disturbances. Methods: Data were collected via an online survey comprising two questionnaires: the Children's Sleep Habits Questionnaire and the Parents' Sleep Habits Questionnaire. Results: Caregivers who completed the survey (n=193) were 86 % female and had a median age of 40 years. Children of respondents were 54 % male and had a median age of 8 years.

Ninety percent of child total sleep disturbance scores were above the clinical cutoff score (>=41), for marked sleep disturbance. However, only 22 % of children had undergone a formal sleep assessment, and only 17 % had been diagnosed with a sleep disorder. Mean child scores for all subdomains (bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, sleep disordered breathing, and daytime sleepiness) were elevated above those of a large historical community sample. Caregiver total sleep disturbance scores and daytime sleepiness scores were significantly correlated with child total sleep disturbance scores (r=0.544, p<0.001 & r=0.413, p<0.001, respectively). Conclusions: Clinically significant sleep problems are present in children with PMS; however, most children have not been formally evaluated for sleep disorders. Further research utilizing objective sleep measures is warranted to identify the underlying sleep disorders present in children with PMS. When properly diagnosed, many sleep disorders can be alleviated with intervention. Addressing sleep disorders may not only improve the child's health and well-being, but also the quality of life of their caregivers.

The Clinical Utility of a Multi-Gene Panel for Neuromuscular Disorders

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1. GeneDx

Objective: To assess the clinical utility of a multi-gene panel for diagnosing a neuromuscular disorder (NMD). Background: NMD encompass over 200 clinically and genetically heterogeneous disorders that primarily affect the peripheral nervous and musculoskeletal systems. Overlapping clinical features can make a clinical diagnosis challenging and may lead to a diagnostic odyssey while potential health risks associated with the condition go unmonitored. Molecular testing using a large multi-gene next generation sequencing (NGS) panel is a newly available diagnostic tool for providing a genetic diagnosis. Methods: In this retrospective study, molecular testing was performed on 150 individuals with NMD using NGS and exon-level copy number analysis of NMD 76 genes. Confirmed test results and clinical information were evaluated to assess the positive rate and concordance with the patient's suspected diagnosis. Positive results were defined as a pathogenic or likely pathogenic mutation in an autosomal dominant or X-linked disorder, or two mutations in an autosomal recessive disorder. Results: The positive rate for the panel was 34 % (49/146). We found that 55 % (27/49) of positive cases were concordant with the clinical diagnosis at the time of testing, while 35 % (17/49) showed discordant results and an alternate diagnosis was established. Examples include limb girdle muscular dystrophy (LGMD) to hypokalemic periodic paralysis, type1 or FSHD to a dystrophinopathy. In 10 % (5/49) no prior clinical diagnosis was provided. Of the positive cases, 38 % had mutation in genes associated with LGMD, and 18 % in genes for congenital muscular dystrophies or myotonias, consistent with the high frequency of these disorders. Counclusion: Our results demonstrate that multi-gene panels for NMD are an effective diagnostic tool and in this series provided an unexpected diagnosis in one-third of cases. Pursuing a multi-gene panel may allow identifying phenotypic outliers, for which potentially therapeutic interventions exist; hence, targeted long-term management of patients can be improved.

VIII. Clinical Care: Pre/Perinatal

Something Extra on Chromosome 5: Couples' Understanding of Positive Prenatal Chromosomal Microarray Analysis Results

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Chromosomal microarray analysis (CMA) identifies copy number variants (CNVs) associated with known syndromes, risk for neuro-cognitive disorders, an uncertain phenotype, or normal development. When diagnosed prenatally, couples' understanding of the nature and consequences of CNVs impacts decision-making and coping. To assess understanding of positive prenatal CMA results, we conducted phone interviews with 28 women (2 terminating pregnancies and 26 continuing) and 13 male partners 4–8 weeks after receiving positive CMA results from genetic counselors. Transcript analysis assessed how CNVs were described, interpreted and understood phenotypically. We compared this with laboratory interpretation (pathogenic, likely pathogenic, variant of uncertain significance (VOUS), or likely benign). We found nearly all the women, but few men, accurately described the chromosome involved, whether the CNV was a deletion or duplication and the range of possible phenotypic effect; all participants knew if it was inherited or de novo. Most participants initially interpreted results as abnormal or uncertain, but couples told a parent carries the same CNV as the fetus re-interpreted results as normal or benign even if classified by the lab as likely pathogenic or VOUS. Some couples receiving VOUS results were reassured by lack of definitive information suggesting a problem, while others wanted probabilities and experienced ongoing concern. When considering possible clinical involvement, couples assessed their threshold for parenting a child with a particular problem, most frequently mentioning learning disabilities and autism risk. These findings suggest women, but not partners, generally understand the nature and clinical implications of prenatal CMA results. Couples feel reassured, perhaps sometimes falsely so, when a CNV is inherited from a "normal" parent. When a CNV is de novo without ultrasound findings, even when some phenotypic information is available, couples experience considerable uncertainty. Research is needed to identify counseling approaches to aid understanding and adjustment to uncertain results.

Patient Responses to cfDNA Testing for Aneuploidy in a General Pregnancy Population: Preliminary Results of the Rhode Island Experience

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Introduction: Several studies support the ability of cell free DNA (cfDNA) to screen for aneuploidy in the general risk population. However, evidence is still sought to support the feasibility of offering this through primary care obstetrical providers. Purpose: To develop a mechanism to educate primary care office staff and to determine if validated educational materials for the general risk patient support informed decision making. Methods: In September, 2014, Women & Infants Hospital of Rhode Island began offering a cfDNA test (DNAFirst) to general prenatal practices. Office education was developed, and patient materials were validated by a focus group. Testing was offered at no charge through an arrangement with Natera, Inc. (San Carlos, CA). One hundred women with negative cfDNA test results were selected for a telephone survey to measure satisfaction, their knowledge of cfDNA testing, and characteristics of their experience. Results: Sixty-six patient surveys were completed to date. Surveys were administered by an experienced genetic counselor, consisted of 36 questions and took 10 minutes to complete. Women responded favorably (89–98 %) to 5 questions regarding the amount of information provided and time allowed to decide. Questions focusing on satisfaction revealed 97 % of women scoring 4 or 5 out of 5 regarding their decision to have the test. All 66 women would recommend the DNAFirst test to others, and 62 (94 %) would choose it again themselves. Responses to knowledge questions were more variable. Around 80 % knew what the test screened for and that there was a small chance of an

affected fetus with a negative screen; 70 % knew that a positive result was not diagnostic. Of 58 women opting for sex aneuploidy testing, 40 (69 %) chose it to learn fetal sex. Conclusions: cfDNA testing can be an acceptable alternative to conventional serum screening. Women express satisfaction with the information they receive from providers and supplemental material. While most women understand test benefits and limitations, there are opportunities to improve knowledge.

NIPS + FTS = ?: A Consideration of the Next Steps of Prenatal Screening

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Introduction: Since its introduction less than 4 years ago, cell-free DNA screening, also referred to as noninvasive prenatal screening (NIPS), has been widely adopted as a screening tool for women at a high risk for fetal aneuploidy. As use expands into the general population, questions arise concerning the integration of NIPS into preexisting screening paradigms. Hypothesis/Purpose: This study aims to examine the use of NIPS in current practice, predominantly in the United States and Canada, in order to inform strategies for the optimal use of both new and existing screening techniques. Methods: We electronically surveyed 208 practicing members of the National Society of Genetic Counselors to ascertain how NIPS is currently being used. Genetic counselors were queried as to the advantages and disadvantages of offering NIPS to all patients regardless of a priori risk. Results and Conclusions: Results indicate substantial variation in practice regarding which patients are offered NIPS and how counselors have incorporated NIPS into existing screening routines. The majority of participants report offering NIPS in conjunction with another method of screening for fetal aneuploidy, indicating that NIPS is being used as an addition rather than as a replacement. These screening methods primarily include nuchal translucency (NT) and maternal serum alpha-fetoprotein (MSAFP) (45.1 %, *n*=78) or first trimester serum screening, with or without an NT, and MSAFP (19.7 %, *n*=34). Further, the majority report that they would be concerned about losing the clinical value of an NT in a complete transition to NIPS (85.4 %, *n*=164). Counselors are evenly split on the merits of expanding the use of NIPS to the general population (con: 55.3 %, *n*=105; pro: 44.7 %, *n*=85). The lack of consensus among respondents suggests that practice guidelines might be a benefit to counselors at this time. In addition, the respondents emphasize the significance of better educating providers about the risks, benefits, and limitations of the test.

Smith-Lemli-Opitz Syndrome is as Common in Caucasians and Ashkenazi Jewish as Spinal Muscular Atrophy: Accurate Carrier Frequencies Identified Through Expanded Carrier Screening

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1. Counsyl

Objective: Smith-Lemli-Opitz syndrome (SLOS) is a profound autosomal recessive disease caused by mutations in the DHCR7 gene. Individuals with the disease may exhibit a wide of phenotypic abnormalities, including multiple congenital malformations, facial abnormalities, metabolic errors, intellectual disability or developmental delay and behavioral abnormalities. Fetal demise is also thought to be a common outcome (up to 90 %) in affected fetuses. Having performed carrier screening for SLOS in a large unselected cohort, here we compare the frequencies of SLOS and spinal muscular atrophy (SMA), a disease currently recommended for pan-ethnic screening based on severity level and high prevalence. Methods: Targeted *DHCR7* mutations were analyzed in 174,156 individuals presenting for routine carrier screening. We compared the resultant carrier frequencies to those published for SMA. Results: SLOS carrier frequencies were 1 in 56 in all combined Caucasians and 1 in 42 Ashkenazi Jewish. By comparison, the published SMA carrier frequency is 1 in 47 Caucasians and 1 in 67 Ashkenazi Jewish.
In other groups, SLOS frequency was less than 1 %, though it did exceed 0.5 % in Hispanics (1 in 168) and African Americans (1 in 175). The SMA carrier frequency in these two latter groups is approximately 0.75 %. Conclusion: SLOS and SMA are similarly severe diseases. SLOS causes intellectual disability and congenital defects, though fetal demise occurs in up to 90 % of conceptuses. SMA results in neurodegeneration and infant death in most cases. Our data show that SLOS is common in Caucasians and Ashkenazi Jewish, relative to SMA frequency. The American College of Medical Genetics and Genomics recommends pan-ethnic SMA carrier screening, due in part to frequency and severity. Given the similar incidence and severity of SLOS and SMA, consideration should be given to routine carrier screening for SLOS, at minimum in the Caucasian and Ashkenazi Jewish populations.

The Experience of Vulnerable Patients Participating in Prenatal Research Following a Diagnosis of Down Syndrome

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A prenatal diagnosis of Down syndrome (DS) brings a range of emotional responses for expectant parents. Given that this is a vulnerable time, medical professionals are met with historical, ethical and practical difficulties for conducting prospective, large-scale studies with the prenatal population. Following completion of an anonymous, web-based questionnaire which explored patients' experiences and needs after a prenatal diagnosis of DS, patients were subsequently asked to complete a self-assessment of their experience with research. The 8-item post-study questionnaire, adapted from a previous bereavement study, aimed to assess the emotional impact, perceived benefits and negative outcomes of the research experience. A convenience sample of 232 respondents, 21–54 years old, from 47 US states and 5 countries, included patients who chose to terminate, continue and parent the child or create an adoption plan. At the time of participation 30 % were currently pregnant. Results showed that 95 % found participation in research to be beneficial, 95 % agreed it provided an opportunity to share their feelings and 96 % felt their participation could potentially help others. While 9 % felt research participation was stressful, 91 % did not. While most agreed their participation had some effect on them, and 28 % experienced unanticipated emotional responses, only 1 % rated the overall research experience as negative or regretted the decision to participate. Furthermore, the majority (72 %) of patients provided personal contact information to learn about future research opportunities regarding their prenatal diagnosis experience. Results support existing literature: even those who experience distress positively evaluated research on sensitive topics and their participation in it. We conclude that the potential altruistic and cathartic benefits of participating in research outweigh the potential risks of psychological distress for patients with a prenatal diagnosis of DS and suggest that research opportunities may be considered as a resource even during vulnerable times.

Prenatal Diagnosis of Down Syndrome: Genetic Counseling as a Significantly Unique Service

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1. Duke University Medical Center

Current literature is limited to retrospective accounts of patients with a prenatal diagnosis (PNDX) of Down syndrome (DS). With increasing popularity of noninvasive prenatal screening (NIPS), the need for further investigation of patients' diagnostic experiences is more important than ever. This exploratory study aimed to assess patients' experiences following a PNDX of DS. Participants voluntarily completed an anonymous web-based questionnaire to characterize the genetic counseling (GC) process and define the role of GC as well as information provided. A convenience sample included 187 men and women, ages 19–49, with a PNDX of DS in 2013 or 2014 via amniocentesis (n=68), chorionic villus sampling (n=28) or NIPS (n=87) in an ongoing or recent pregnancy. Responses were stratified and compared by logistic regression based on whether there was interaction with GC. Most patients (n=120) had some interaction with and 59 % (n=71/120) were initially told the PNDX by a GC. The GC role was more frequently considered to be "educator," providing mostly genetic or medical facts about the diagnosis (63 %) and less often "counselor" (31 %) or emotional "supporter" (41 %). Compared to various other healthcare providers (HCPs), patients with GC interactions were significantly more likely to receive information about the genetics, associated physical features and intellectual disability, future reproductive options and recurrence risks, potential impact on the family, web-based and printed informational resources including support groups and organizations, and the option to create an adoption plan. Patients with GC interactions were more likely to discuss personal knowledge or beliefs about DS and were also significantly more satisfied with the information and emotional support received. Results represent a novel and current look into patients' PNDX experience and evince GC as a significantly unique service compared to other HCPs. Findings may be useful for demonstrating utility of and justification for the inclusion of GC for a PNDX, with application to other clinical settings.

Posters

I. Access and Service Delivery

A Glimpse into the Future: Disclosure of Genomic Sequencing Results by Non-Genetics Physicians

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Introduction: Experts have raised concerns about a shortage of genetics professionals to interpret/communicate genome sequencing (GS) results, but little data exist regarding GS disclosure competency by non-genetics physicians. The MedSeq Project explores the incorporation of GS into clinical medicine, enrolling primary care physicians (PCPs) and cardiologists to return genome reports (GR) to patients without the mediation of genetic counselors (GCs).
Purpose: Our goals were to assess physicians' intended and actual use of an on-call Genome Resource Center (GRC), staffed by GCs and clinical geneticists, to support their GR interpretation and implementation and to monitor for errors and miscommunication about GS results during GR disclosure.
Methods: At study start, physicians completed a genomics education module. Prior to patient enrollment, physicians were asked about their anticipated use of the GRC. Interviews were consensus coded and analyzed and GRC utilization tracked. Disclosure sessions were recorded and transcripts reviewed for the accuracy of genetic information shared with the patient. If miscommunications were identified, physicians were contacted immediately or at the end of the study depending upon the perceived urgency and safety impact of the miscommunication.
Results: Of 18 physicians asked, 13 articulated an intention to utilize the GRC. Six physicians contacted the GRC in the first 28 months of the study. Of the first 45/100 GS disclosure transcripts reviewed, 20 minor miscommunications were identified for end-of-study educational follow-up, and 3 for real-time intervention (2 related to carrier risk, 1 to inheritance pattern mis-interpretation).
Conclusion: Non-genetic physicians who participated in MedSeq acknowledged the value of the GRC, but only a minority utilized it. While the genetics information provided by non-geneticists contained some errors, serious errors were infrequent. When provided with genetic education and resources to easily query experts, non-genetics providers may be able to correctly and safely convey GS results.

A Unique Service Delivery Model for Genetic Counseling Services

E. Denne[1], M. Gilats[1], G. Lazarin[1], J. Goldberg[1]

1. Counsyl

The recently published joint statement, "Expanded Carrier Screening in Reproductive Medicine - Points to Consider" highlights the importance of post-test genetic counseling in helping patients understand their carrier screening results. Counsyl, a laboratory which has performed expanded carrier screening on over 400,000 patients since 2009, has integrated genetic counseling into expanded carrier screening services since inception, and developed a unique service delivery model in order to scale this service with mass population utilization. Upon results availability, providers are first notified; then, patients are contacted by email and are requested to view their results. Patients log into their secure account online to view results, watch tailored informational videos and request immediate genetic counseling with our on-call service. Patients may also opt to schedule a consult at a later point if preferred. This system may help overcome barriers such as limited access to in-person genetic counseling in certain geographic areas, employment conflicts, long wait times for scheduling an in-person genetic counseling appointment, and appointment times outside of normal business hours. We recently issued 16,306 laboratory results via this unique system, and greater than 90 % of reports were for expanded carrier screening. Currently 79 % of all individuals view their results within 2 weeks after availability. Most that do not view results have no abnormal findings. 99 % of individuals with abnormal results scheduled counseling, declined a consult or received manual follow-up from our support team within 2 weeks. We will present further data to discuss the efficiency of this protocol and the differences in consultation goals compared with a "traditional" model. Understanding these differences will highlight how alternative service delivery models, such as the one we have implemented, help to extend genetic counseling services to an expanded patient population.

Evaluating the Impact of Group Genetic Counseling Sessions in the BRCAcommunity Study

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The purpose of this study was to design, implement, and evaluate the utilization of a group genetic counseling tool and pre-counseling

education among "low risk" Ashkenazi Jewish (AJ) individuals being offered population screening for BRCA founder mutations. Screening is offered through an ongoing IRB approved study called the BRCAcommunity Study, an initiative of the Program for Jewish Genetic Health and Montefiore Medical Center. Methods of pre-test genetic counseling in large groups of low risk individuals are not well defined and have not been previously studied. The counseling tool developed is a PowerPoint presentation containing education about BRCA mutations, two facilitated discussion components, the genetic testing consent process and information about the BRCAcommunity Study. Broad educational themes included the role of BRCA mutations in cancer development, risk assessment challenges in low-risk families, risk-reducing options for BRCA carriers, and risks, benefits and limitations of BRCA testing. Self-administered pre- and post-group counseling surveys were used to determine the effects of the pre-counseling educational materials and group genetic counseling on gains in knowledge and patient comfort. Approximately half of participants indicated they utilized the pre-counseling educational materials 6/11 (55 %). The average pre-counseling knowledge score was 79.5 % while the average post-counseling score was 95.5 %. When asked if they would prefer meeting with a genetic counselor one-on-one: 4/9 (44 %) felt neutral; 5/9 (56 %) disagreed/strongly disagreed. None of the participants preferred to meet with a genetic counselor one-on one. In terms of the interactive elements of the session, 7/9 (78 %) reported feeling comfortable, but only 1/9 (11 %) felt it enhanced the session. This study reveals a broadly positive patient experience using group genetic counseling as an effective service delivery model for population based pre-test genetic counseling in low risk individuals in terms of knowledge gain, patient comfort, and patient perceptions of efficacy.

Facilitating the Continuum of Care: A Model for Utilization of the Electronic Medical Record to Transition Patients from Perinatal to Pediatric Genetics

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With the rapid technological advancement in prenatal ultrasonography, patients are increasingly being identified in the perinatal period as needing postnatal genetic evaluation or testing. With this ever-growing need, it is imperative to improve communication between genetic colleagues in the departments of obstetrics and pediatrics. More specifically, providing and reviewing patient-specific information with the postnatal genetics team so that the patient "handoff" can be successful between departments. At Vanderbilt Children's Hospital genetic counselors in the Departments of Obstetrics and Pediatrics have collaborated to create a communication tool within the electronic medical record (EMR) called the Fetal Center Panel (FCP). The FCP is a list of expecting mothers whose unborn babies have an indication for postnatal genetics evaluation. The panel grants electronic access to the mother and newborn charts and has a brief summary of prenatal information including pertinent labs, ultrasound findings, EDD, delivery plan, and psychosocial information for review by the postnatal team. The providers from the two departments have established the criteria for which patients should be added to the FCP. The prenatal genetic counselors consult with the indicated families and make them aware of the involvement of genetics at delivery while obtaining consent for genetics involvement. Typically these patients have ultrasonography findings consistent with a possible genetic disorder, a pertinent family history, or the need for postnatal testing coordination, including pathology and specialty testing. Both teams monitor the FCP for anticipated and impending deliveries. Having the FCP and summaries electronically accessible facilitates the coordination of care by the pediatric genetic counselors. Consultations are triaged and the pediatric genetic counselors expedite critical labs ensuring they are sent appropriately. The development and use of the FCP within the EMR provides a communication bridge between prenatal and postnatal genetic services and continuity of patient care.

Community-Based Cancer Genetics: Evaluating the Planned Parenthood System

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Well-documented health disparities exist in the provision of cancer genetics services. In response, Planned Parenthood (PP) developed a novel breast cancer risk screening program (BRSQ) to identify clients that could benefit from genetic services. This research evaluated the BRSQ's efficacy as a community-based high-risk cancer screening program. A mixed method approach was used to evaluate clinician knowledge, confidence and utilization of the BRSQ. Novel surveys probing these topics were administered to Mid/South Michigan PP providers (n=14). Descriptive statistical analysis formed the basis for follow-up semi-structured interviews (n=6). An iterative coding process with 3 coders identified themes describing facilitators and barriers to BRSQ and genetic service utilization. The survey and interview results found that all providers knew how to administer the BRSQ and most (83 %) could accurately describe genetic counseling/testing, however they were least confident discussing genetic services with their clients (p<0.01). 6/6 interviews identified limited knowledge of client's family history as a barrier to BRSQ-risk assessment, with specific concerns regarding client awareness of ovarian cancer family histories (6/6) and genetic testing (5/6). Barriers including affordability (6/6), client attitudes towards genetic knowledge (6/6), and background genetic knowledge (5/6) were similar to those in hospital settings. The client population's young age (70 % under age 30) was described in 83 % of interviews as a unique challenge. However, family experiences with cancer was reported as a predictor of clients' interest in seeking genetic services (4/6 interviews). Effective use of a community based cancer screening program depends on both provider and patient characteristics. Provider training should include education about genetic counseling to build confidence and encourage patients to seek genetic services. Understanding the traditional and unique barriers identified in a community setting allows for targeted interventions to improve utilization of genetic services.

Be Careful What you Wish For: The Downstream Impacts of Genetic Counseling Licensure

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1. JScreen, Emory University

Efforts to pass licensure legislation for genetic counselors have proven successful in over twenty states. Licensure protects the public interest, and has led to improved recognition of the profession and reimbursement for genetic counseling services. However, further consideration of the downstream impact is warranted. JScreen is a small, non-profit public health initiative at Emory University dedicated to promoting preconception reproductive carrier screening. The telegenetics approach allows us to reach individuals in remote or underserved areas across the United States. Post-test genetic counseling, provided using phone or secure video-conferencing, is an important part of the service we offer. Our goal is to have at least 2 genetic counselors licensed to provide counseling in every state at all times. Initial application fees and associated costs have totaled over $2,000 per counselor and involved over 40 hours of work to fulfill requirements, many of which are common between the states.

Regular renewal of licenses is similarly cost-prohibitive. These costs do not include those related to continuing education and board certification. Licensure requirements disproportionately hurt smaller non-profit companies over for-profit companies with many genetic counselors on staff. As genetic counselors in additional states succeed in obtaining licensure, the burden in terms of cost and time may lead to reduced ability to serve states with smaller populations and limit telehealth opportunities for the genetic counseling profession as a whole. Reciprocity and other solutions to reduce this growing burden must be a larger part of the licensing conversation.

Greater Professional Autonomy and Recognition with use of a Novel Genetic Counseling Service Delivery Model in a Pediatric/General Genetics Clinic Setting

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1. Beaumont Health

A novel genetic counseling service model in a pediatric/general genetics setting is presented in which patients are seen first by the genetic cousnelor (GC) with the physician evaluation and management (E/M) visit occurring a later time. A GC visit is required prior to any E/M visit. Although GCs in other clinical areas have provided independent GC services for some time, this type of model in the pediatric/general genetics setting is novel. We began incorporating this model in April of 2014, with full implementation by the end of 2014. Professional advantages to the GC have included increased autonomy and recognition of the genetic counselor as a distinct and unique provider. Traditionally, the services of the GC is included as part of the E/M visit. The GC, although considered to be integral to the service, not been recognized as an independent provider and generates no separate revenue. Furthermore, a large portion of the GC's time is spent triaging cases by phone, activities that require separate documentation and are usually not reimbursed. In this new model, the GC is independently responsible for the GC visit including written documentation, correspondence, follow-up, and billing. Most of the triaging is now performed as part of the GC visit so that the documentation is included as part of the GC clinic note and part of a billable service. Because the documentation of the GC visit is separate from that of the E/M visit, other providers are more likely to recognize the GC as an independent provider rather than support staff. Importantly, since the billing of the GC visit is under the GC's national provider identifier number, the revenue cycle at our institution has begun to recognize GCs as a separate source of revenue, which we hope will lead to increased valuation of the GC and genetic counseling services by the institution.

Texas Physicians' Awareness and Utilization of Genetic Services

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The number of disorders for which genetic testing is available has increased nearly 500 % in the past 15 years. Access to the majority of genetic tests and services hinge on physicians' ability to identify patients at risk for genetic disease and provide appropriate testing and counseling or refer to genetics specialists. Recent research demonstrates the need for referrals to genetics specialists by showing that many physicians lack skills required to perform appropriate genetic services, such as making proper risk assessments, providing genetic counseling, ordering genetic testing and interpreting results. However, little research exists on physicians' awareness and utilization of genetic services. In this study, an electronic survey evaluating practicing physicians' awareness of, utilization of, and perceived barriers to genetic services in Texas was distributed via state physician organizations. Of the 157 participants, approximately half reported they were moderately or very aware of genetic testing and services in their area. Very few reported awareness of telemedicine services. Over two-thirds reported never or rarely referring to genetic counselors or other genetic specialists, despite 75 % reporting they had noticed an increased impact of genetics on their field and 61 % reporting they had discussed genetics more in their day-to-day practice in the last 5–10 years. Only 20 % reported genetics was very integral to their specialty. Over three-fourths of all participants indicated interest in learning more about genetics, genetic testing and genetic services. Among the most frequently chosen barriers to genetic counselors were awareness-related barriers such as not knowing how to refer to a genetic counselor. Responses to many items varied significantly by medical specialty. The results identify a need to increase awareness of genetic services and referral logistics. Specific findings can help direct outreach efforts to educate clinicians, such as developing clinically meaningful, specialty-specific educational objectives.

Next-Generation Counseling: Increased Efficiency and High Patient Satisfaction Utilizing Web Technology and Telephone for Post-Carrier Screen Counseling and Education

G. Lazarin[1], M. Gilats[1], E. Denne[1], I. Haque[1]

1. Counsyl

Post-test patient followup is integral to carrier screening programs. However, there are 4M pregnancies each year and expanded carrier screening (ECS), which confers high test-positive rates, is being increasingly utilized. Thus, efficient allocation of genetic counselors' (GCs) time is a necessary step to large-scale implementation. Our laboratory has offered iterations of direct-to-patient results delivery. Here we compare three models' effects on GCs' time spent: V1 (every patient speaks to a GC), V2 (results are systematically triaged, and most patients are given results online, with web education and immediate GC consultation option), and a "traditional" model (the clinic delivers results and GC consultation is available when initiated by the patient). We analyzed consultation uptake, duration and satisfaction for 304,108 carrier screening results issued by our laboratory, identifying the following trends: (1) In all versions, more serious results (e.g., a carrier/carrier couple) were associated with longer consultation times. (2) In V2 and the traditional model, more serious results were also associated with higher consultation uptake rates. (3) Consults were longer on average for V1 results than for V2. E.g., an individual carrier consult was 12 min (9–17 min, interquartile range) for V1 and 10 min (7–15 min) for V2. The shorter consult times may derive from pre-consult web education issued through V2. (4) Illustrating optimal GC allocation, the V2 website education provided for negative results enabled lower consultation rates compared with V1. (5) Patient satisfaction was high (4.9 / 5.0 rating) in all models. We demonstrate time utilization benefits by a results-delivery model that combines web education and counseling. Time saved by efficient delivery of simpler results offsets time used due to increased positives. In one example, 2 minutes per consult were saved. As a laboratory issuing multiple thousand results per week, with concomitant GC availability, this translates to hours saved enabling feasibility of post-test follow up for widespread ECS.

Participant Perspectives and Efficiency of iPads in Pedigree Construction and Assessment

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2. HCA Healthcare

Many medical institutions have converted to using electronic health records (EHR). Numerous programs have been created to draw pedigrees, yet integration of these programs into EHRs remains limited. Anecdotally, many counselors still construct pedigrees using pen and paper, while others use available commercial software. To date, there has been little research comparing methods. The goal of this study was to assess the experience of participants when having their family histories taken with pen and paper compared to a digital method (Proband©) on the iPad. Forty-eight participants were recruited from a university student and faculty population and were randomized to a pen and paper group or iPad group. Outcomes assessed included: time needed to draw the pedigree, plans for sharing the information, perceived accuracy, and satisfaction with the process. Pedigrees were recorded by the primary author. There was no statistically significant difference found on any outcomes measured between the two groups, as analyzed by two-tailed Fisher's exact test. Specifically, no difference was found in the amount of time needed, and 94 % of participants reported being satisfied with the experience. In spite of providing education about the importance of family health history information, only fourteen participants (29.2 %) indicated that they would share the pedigree with family members. All in the iPad group (24/24) and 22/24 in the pen and paper group reported satisfaction with accuracy of the pedigree. Although this difference was not statistically significant, the perception of increased accuracy in the iPad group may be an area for future study. Recording pedigrees using an electronic method may increase efficiency in clinical care if the method can be seamlessly integrated with EHR. Results from this research show use of the iPad application does not negatively impact perceived accuracy, rapport during the pedigree, or overall satisfaction. This study provides evidence to support use of iPad applications for collection of family health history in clinical settings.

Cancer Genetic Counseling by Videoteleconferencing Along the Texas-Mexico Border

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Breast and colorectal cancers are two common cancers for which genetic risk assessment and counseling are available. However these services are often limited to major metropolitan areas and not frequently accessed by underserved populations. Multiple ethnic and racial disparities exist with regards to identification of high-risk individuals, screening, and treatment outcomes; these socioeconomic factors are frequently seen in minority and new immigrant populations. We provided cancer genetic risk assessment and counseling via telemedicine, as well navigation to breast and colorectal cancer screening, education, and outreach to the south Texas-Mexico border region. This population shares many of the barriers identified in other minority populations, including lack of resources and health insurance, distrust of the medical system, and family and employment obligations that preclude access to care. In order to determine the acceptability of this alternate service model, program participants were mailed a 20-item questionnaire to assess their level of satisfaction with the program. With a completion rate of 34 %, the overall level of satisfaction was very high (4.715 out of 5), and nearly half reported decreased concerns about developing cancer after genetic counseling. These findings demonstrate the acceptability of a cancer genetic risk assessment program heavily reliant on telemedicine in an underserved minority community. Despite the challenges previously noted in the literature about serving minority populations and barriers to cancer genetic risk assessment for Hispanics, we were able to provide these services in line with traditional genetic counseling services while maintaining a high level of participant satisfaction.

Making Sense of a Primary Care Role in Genomic Medicine: Views of Genetics Health Professionals

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Developments in genomic medicine (GM) are expected to implicate primary care providers (PCPs), who, as first contact professionals with a foundational role in most health care systems, will need to be equipped. Yet public policy efforts to enhance the relationship between primary care (PC) and genetics are inconsistent or non-existent. Purpose: To explore the role of genetics health professionals (GHPs) in building relationships with the PC community. Methods: Qualitative methodology. GHPs at centers across Ontario, Canada were invited to participate in semi-structured focus groups or telephone interviews. Purposeful sampling was used to ensure diversity by type of GHP and of center (academic, community). Transcripts were analyzed using a qualitative interpretive approach. Results: 5 focus groups and 2 interviews were conducted (6 clinical geneticists, 24 genetic counselors, 4 nurses, 4 lab staff, 3 administrators) from 5 of 10 regional genetics centers and 2 of 5 northern outreach clinics. Participating GHPs expect PCPs to play a role in GM and describe the relationship between GHPs and PCPs as key to the provision of quality GM. However through interactions with their patients and very limited direct interactions with PCPs, GHPs expressed limited understanding of PC scope of practice and acknowledged uncertainty about how GM might fit into primary care practice. GHPs voiced concern about a perceived lack of knowledge of GM, as reflected in under- and over- referral, and in PCPs ' ability to incorporate new genomic discoveries. GHPs also reflected on whether existing communication methods with PCPs were effective, and recognized a need to understand PCPs' need for support in this area. Conclusions: GHPs recognize an important role for PCP in GM, but in the absence of policy direction or organizational support, they struggle to make sense of how this might work. In this context, in addition to identifying knowledge and capacity deficits, parameters of a productive collaboration between PCPs and GHPs need to be developed.

A Genomic Education/Decision Support Tool for Clinical Sequencing

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1. University of Michigan

Genomic medicine challenges health care providers to communicate complex information. Of particular importance is the task of obtaining informed consent (IC) for clinical sequencing (whole genome/ whole exome sequencing (WES)), which has relevance for the diagnostic evaluation as well as implications for additional health considerations known as secondary findings. Tools for facilitating IC and decision-making in this context are limited. We therefore developed an education/decision support tool in a personal narrative/video format to enhance communication, IC, and to assist with identifying patient preferences for the return of results. The experience of a family undergoing clinical sequencing, decision making and receipt of both diagnostic and secondary test results was used to highlight issues for consideration during the IC process. The 8-minute video is viewable prior to a patient's appointment or in clinic via

an iPad. Family specific questions and concerns are addressed by the genetic counselor when the video has ended. Forty-six families (n=81) completed an anonymous, novel 8-item Likert scale survey examining knowledge, self-rated understanding, clarity, and ease of choice. The validated Traditional Decisional Conflict Scale (DCS) was used to examine the factors of certainty, values clarity, knowledge, and confidence in decision making, with scoring from 0 to 100. The majority (60 %) reported the video tool assisted with decision making, while 32 % were neutral. Total average score on the decisional conflict scale (7.16) was consistent with minimal conflict. The average length of time for WES counseling and informed consent was 21½ minutes (range 15–40), not including time for viewing the video. Our findings show that an education/decision support tool can be invaluable as an adjunct to counseling and informed consent for genomic sequencing. Understanding of sequencing-specific issues and test outcomes, and confidence in decision making with minimal conflict are achievable within the clinical setting.

Genetic Telecounseling: Ensuring Quality Patient Care by Examining Initial Experiences

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1. Recombine

As the technologies and methodologies for genetic testing evolve, so must the careers surrounding it. With a welcome push from the larger medical community to integrate genetic testing into routine care, genetic counselors in particular find themselves providing patient care in new and different environments. With an increasing number of genetic counselors employed by laboratories, the practice of telecounseling is becoming more commonplace. Limited literature exists in regards to strategies or recommended practices for a successful genetic telecounseling session. Just as standards of care were constructed in the past for clinical genetic counseling, the same must now occur for telecounseling.

Important aspects of a clinical counseling session, such as establishing rapport, explaining complex genetic concepts, obtaining a detailed family history, and coordinating follow-up care will need to be successfully incorporated without the added benefit of face-to-face interaction. A number of laboratories currently offer post-test telecounseling following expanded carrier screening, noninvasive prenatal testing, and hereditary cancer screening. These sessions vary greatly in their structure and the incorporation of the aforementioned clinical elements. It is important that counselors with vast experience performing genetic counseling via telephone and other communication technologies discuss what works, what could be improved, and what inherent issues cannot be eliminated. In doing so, practice guidelines that prove successful universally can be established. By examining the initial experiences of a team of laboratory genetic counselors conducting genetic telecounseling for both expanded carrier screening and noninvasive prenatal testing, our aim is to start a dialogue to lay the groundwork for the establishment of telecounseling practice guidelines.

Partnering with Industrial Engineering to Obtain Critical Programmatic Resources

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1. Illumina
2. University of Michigan

Problem: The increasing demand for clinical genetics expertise, specifically in regards to the growing patient volumes and the institutional goal of decreasing patient appointment wait time, placed stress and strain on the genetic counselor and physician resources at the University of Michigan Medical and Cancer Genetics Clinics. We partnered with an industrial engineer (IE) to identify ways to streamline workflows and delegate specific tasks in an effort to meet these demands. Intervention: Between March and March 2014, the IE mapped clinic workflows, interviewed GCs, support staff and scheduling teams. Data from a previous GC time study was also utilized. The goal was to propose streamlined workflows that respect unique clinical requirements, and determine the full time effort (FTE) requirements for execution. Solution: The IE proposed: 1) centralizing intake to a single individual supporting the two clinics, ensuring individuals speak with a knowledgeable person and patients are scheduled appropriately. 2) Delegating insurance authorization for the clinic visit and genetic testing to a single individual 3) ordering pre-assembled appointment packets for patients and 4) Delegating administrative tasks including, mailing/collecting clinic forms, obtaining outside medical records and patient no-show/cancellation follow-up. The IE recommended 1.5 FTE "intake coordinators" and 0.75 FTE for insurance authorization. The IE provided the institution with detailed documentation and this proposal was approved with an additional 0.5 FTE granted (2.75 FTE) to accommodate for anticipated growth.

Outcome: Since implementation, both clinics have experienced increased patient volume and decreased wait times. The physicians and GC's report that the daily clinic operations have improved and streamlined with appropriate patient scheduling and the upfront work of gathering medical records and insurance information. Partnering with the IE allowed for the collection of systematic, detailed data demonstrating needs and obtaining necessary resources.

Fetal Center web Directory Provides Easy Access to Fetal Center Genetic Counselors

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2. Vanderbilt University

Since the publication of the results of the Management of Myelomeningocele Study (MOMS) in 2011, there has been a surge in ultrasound units rebranding and reinventing themselves as Fetal Centers. Fetal Centers typically utilize a multidisciplinary approach for the evaluation and management of women with pregnancies diagnosed with a fetal anomaly by ultrasound. Some centers offer fetal interventions.

Genetic counselors have worked in the area of obstetrics and ultrasound for decades and are experts at providing education and discussing testing options to families receiving news of a potential fetal anomaly by ultrasound. However, it has been difficult for patients and providers to easily identify Fetal Centers which employ genetic counselors as part of their multidisciplinary team. With grant funding from the Prenatal Special Interest Group (SIG) of the NSGC, the REDCap web application was used to create an online database of Fetal Centers. Patients and providers will find 53 Fetal Centers listed in 26 states at www.NSGC.org/fetalcenterdirectory. Links to the centers' websites are provided as well as their contact information. All contributing centers were polled for the fetal anomalies for which they provide evaluation and fetal interventions. These data are listed as well as the diagnostic procedures offered. Data regarding support services available (social work, housing assistance, perinatal palliative care) and if patients are being recruited for fetal intervention studies are also provided. Members of NSGC have the exclusive ability to download contact information for genetic counselors working at each Fetal Center. This online directory is an excellent resource for those seeking Fetal Center services. It highlights the value of Genetic Counselors in this growing area of expertise. The website will be maintained by the NSGC and updated annually by the Prenatal SIG prior to the educational conference to keep the information current and inclusive of all Fetal Centers with genetic counselors.

Barriers and Motivators for Genetic Counseling Services: A Physician Survey

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1. Cleveland Clinic

The practice and billing of genetic counseling services have evolved in recent years with the hope of providing greater access. Referral practices of physicians to genetics have been previously studied with the greatest emphasis on referrals to genetic services in general or to cancer genetics. Primary care physicians have most commonly been surveyed with a few surveys including specialists. The objective of this study was to gain a better understanding of what influences physicians to utilize genetic counseling services at Cleveland Clinic as well determine the obstacles in referring to genetic counseling in order to increase patient referrals. An electronic survey was distributed to 934 physicians in the Heart and Vascular Institute, Pediatric Institute, Neurological Institute, Cancer Institute and OB/GYN and Women's Health Institute of the Cleveland Clinic Health System. The survey consisted of a maximum of 36 questions regarding knowledge and awareness of genetic services, existing referral practices, motivators and obstacles to referring patients. Descriptive statistics were used to analyze and summarize the study responses. Ninety-four percent of physicians from select institutes indicated they were aware of genetic counseling services and 75 % of physicians who have referred to genetic counseling services were "very satisfied." Fourteen percent of respondents indicated a "completely sufficient" understanding of how genetics can meet their current practice needs. The greatest barrier to referring to genetic counseling services was the cost of tests (51 %) and genetic counseling (43 %). Following cost, 27 % of physicians agree that patient willingness is a barrier to genetic counseling services. Thirty percent agreed that accessibility of services was a barrier. The results of this study indicate the need for ongoing education of physicians and patient groups and to provide services in locations that are convenient for the patient.

What We Have Learned and What We Need to Change: Two-Year Experience of a Newly Established Prenatal Genetics Clinic in Japan

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1. Fetal Medicine Clinic Tokyo

Since 2013, we have established a new prenatal clinic in Tokyo. Founding members were a fetal medicine specialist as well as a clinical geneticist, and a genetic counselor, and both studied in Europe and the U.S. We have practiced according to the European and American standard, providing full-spectrum of prenatal testing/diagnosis, including first and second trimester screening, detailed sonogram, chorionic villus sampling, amniocentesis, and genetic testing when needed, with sufficient individual and group genetic counseling sessions. Although it has been reported that prenatal testing is not commonly practiced in Japan, we have seen more than 3,000 people over 2 years, and have learned many things from their statements. In this presentation we would like to describe what we have learned. First of all, there is a short supply of prenatal testing in Japan, and equal access for people is not guaranteed. Many have faced difficulty to have prenatal testing because there are not many providers, and obstetricians often try to stop them undergoing prenatal testing because it is an unethical thing. Second, prenatal practice seems not to be standardized in Japan. Different providers have different procedures, and many use different risk assessment calculations. Third, complexity of genetics seems not to be understood by most of Japanese practitioners, as they tend to ignore people's family histories and genetic backgrounds. Fourth, as we experience that information provision through our genetic counseling has been greatly appreciated by clients, it seems that information about prenatal options is very limited among pregnant women and couples, as well as among medical professionals. Although there are many challenges in Japan in this field, the first thing we need to do seems to be introduction of the idea of people's right to obtain information, right to choose, and guaranteed equal access to the prenatal testing options. We would like to promote people's self-determination and informed choices, and expand our online information provision, in addition to genetic counseling at our clinic.

Genetic Testing "Pain-"Perwork: Improving the Collection and Submission of Clinical History for Genetic Test Orders

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1. Seattle Children's Hospital and the Pediatric Laboratory Utilization Guidance Services
2. PreventionGenetics

Clinical history is critical for accurate and meaningful genetic test result interpretation. Despite reference laboratories' requests for this information, it is not routinely submitted. When omitted, laboratory directors may be limited in their ability to pre-analytically review test requests for appropriateness, interpret results, or produce a report that offers meaningful interpretation and recommendations. When reference laboratories spend time eliciting this information from ordering providers, test delays may result. We identified several barriers to consistently submitting clinical history on genetic test requisitions, including unique requisitions across labs and limited provider/staff time to locate and complete requisitions. The purpose of this study was to outline the current landscape and develop and implement a standard clinical history form to be included with test requisitions. We hypothesized that use of a standardized, simplified form would increase the number of requests that include clinical history and enable reference laboratories to better review orders, ultimately improving the value of test request and interpretation. A 1-month retrospective review was completed to determine how often clinical history was provided on genetic test requisitions. Of 74 requisitions, 8 were excluded due to explicit clinical history requirements (e.g., exome sequencing) and the proposed form would not apply. Only 29 % (19/66) of the requisitions included clinical history. Genetics providers' orders included clinical history on 42 % (19/45) of requisitions; non-genetics providers' on 0 % (0/21). The value of clinical history for genetic test interpretation is generally recognized. A standard clinical history form may improve the inclusion of this information with genetic test orders. We created a form modeled after the International Collaboration for Clinical Genomics patient history form, reviewed it with several reference laboratories who affirmed that it would satisfy their needs. The standard form is being piloted with our institution's genetics providers with a plan to expand use by other providers.

Developing a Cancer Genetic Counseling Service at an Institution Serving Minority Populations: The Howard University Cancer Center Experience

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Washington, D.C. has one of the highest breast cancer mortality rates in the country – 26.3 per 100,000 compared to a national rate of 21.5 per 100,000, and higher breast cancer incidence rates for women under age

50 versus the U.S. average. Of note, evidence shows that African American (AA) women with triple negative breast cancer (TNBC), an aggressive subtype of breast cancer, have worse clinical outcomes than Caucasian women. U.S. Census data for D.C. shows that nearly 60 % of its 649, 111 residents are AA or non-White Hispanic, making D.C. one of the most diverse populations in the U.S. and a unique location for cancer genomic activities. At this institution, over 50 % of minority women with breast cancer and/or a family history of cancer participating in research studies met the National Comprehensive Cancer Network's guidelines for further genetic evaluation/testing. Due to the high breast cancer mortality/incidence rates in young, ethnically diverse women, the prevalence of TNBC, and the collection of family health history at this institution, the need for genetic counseling and testing was identified. We will discuss how this new service was developed at an institution providing care for minority populations. Acquiring a culturally-competent minority genetic counselor was vital, as data suggests that minority genetic counselors and health care providers (HCPs) increase the uptake of genetic services amongst minorities. Educating HCPs on the importance of genetics as it pertains to patient management-of-care has assisted with referrals, patient compliance, and the overall implementation of the genetic counseling service. As a result, this institution has increased the uptake of cancer genetic counseling services by nearly 40-fold, from 2 to 3 patient encounters per year to over 200 patient encounters within a 21-month time span. Furthermore, referrals continue to increase from outside institutions due to community engagement and outreach.

Benchmarking the Process of Genetic Testing Insurance Authorization in a Large Academic Medical Center

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Introduction: The rapid expansion of available genetic tests (GT), increasing number of testing laboratories, and differences in insurance coverage has led to a complicated, time-consuming GT insurance authorization (IA) process. This process is confusing to patients and clinicians and is a barrier to obtaining appropriate genetic services. We aimed to benchmark the GT IA process and ascertain optimal work-flows. Methods: Baseline surveys and follow-up interviews were conducted by an industrial engineer and patient services associate (PSA) with representatives from 8 genetics and 4 specialty clinics at the University of Michigan. Questions regarding each clinic's scope of GT and current IA process were developed by the industrial engineer, genetic counselors (GCs), and PSA. Results: Clinics surveyed order 1 to >20 GT each week. None of the clinics routinely obtain GT IA prior to the appointment. Seven clinics write letters of medical necessity, while three clinics include GT IA information in the clinic note. In seven clinics, the clinician is responsible for determining insurance coverage, accomplished by asking the patient/hospital billing staff/other administrative staff, checking the electronic medical record, or calling the insurance company. In eleven clinics, patients must return for sample collection following IA. Sample collection is only done the same day if patients have IA or are having DNA extracted and held by the testing laboratory pending IA. In nine clinics, the physician or GC is responsible for submitting the necessary IA documentation, following-up on pending IAs, and notifying patients of GT coverage decisions. Conclusion: The results of this benchmarking study showed that GCs and physicians are responsible for several of the tasks associated with the IA process. Delegation of IA tasks to non-clinicians and improving workflows is necessary to reduce clinicians' time spent on insurance authorization and facilitate patients having genetic testing in a timely manner.

II. Adult

Communication Strategies Utilized by People with NF2 and Hearing Loss

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The hallmark of neurofibromatosis 2 (NF2) is bilateral vestibular schwannomas (VS), which cause hearing loss (HL) that progresses to deafness typically beginning in early adulthood. Incomplete auditory rehabilitation following the onset of HL can lead to significant interruption in communication across multiple spheres of life. There is little known about the strategies for communication utilized by people with NF2 and HL, or the adequacy of these methods. A 14-question online survey was advertised to individuals with NF2 and HL through NF2 support groups with an online presence and several NF2 clinical centers in the United States. Survey responses were collected and analyzed. 187 participants from 5 continents were eligible for inclusion in data analysis. The mean age of respondents was 39 years. The average duration of HL at the time of the survey was 13.6 years (SD=9.6). Most individuals reported using a combination of strategies for communication. The majority (125/187) utilize lip reading. 41 % (76/187) use manual signing, such as a formal sign language, cued speech, fingerspelling, or "homemade" signs. Only 4 respondents rely solely on a formal sign language to communicate. 14 % (27/187) use written language to supplement their communication. Despite the numerous strategies employed, 95 % of respondents report ongoing communication difficulties in one or more daily settings.
Auditory rehabilitation in the NF2 population is currently inadequate even in the context of improved rates of hearing preservation following surgery, moderate success with medical therapies, and amplification options (e.g. hearing aids, cochlear implants, auditory brainstem implants). Importantly, the uptake of sign language as a primary means of communication in the NF2 population is very low. Clinicians should be aware of the range of communication strategies employed in this population, as well as the reported inadequacy of these options. This data also speaks to the need to develop alternative methods of enhancing communication for people with NF2 and HL.

The Diagnostic Process of Ehlers-Danlos Syndrome and the Symptoms Leading to the Diagnosis: A Pilot Study of 25 Rheumatology Patients

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Ehlers-Danlos syndrome (EDS) is a collagen deficiency disorder that affects multiple organ systems, including the cardiovascular, skeletal, and integumentary systems. Due to the different multisystem presentations of at least six major subtypes, other studies have shown that EDS is commonly underreported, misdiagnosed, and that a true diagnosis can be delayed by decades. The purpose of this study was to comprehensively explore the difference between the signs for diagnosis and symptoms presented by participants leading to the diagnosis of EDS in a group of patients followed by rheumatologists for joint pain or other rheumatologic reasons. Twenty-five, english-speaking participants (18-years-old or older) diagnosed with EDS were recruited from rheumatology clinics at one medical center and were interviewed in person or by phone by the first author. The interview included a survey of 108-dichotomous questions on symptoms associated with EDS. Patients were also asked age of

onset of their symptoms, which medical specialties they had seen, and what symptoms led to their diagnosis of EDS. Study participants identified as having EDS subtypes hypermobile (48 %, *n*=12) or classic (20 %, *n*=5). Mean age of diagnosis was 33.5 years (range 20–63 years) and duration from onset of symptoms to diagnosis averaged 24.6 years. Participants reported being diagnosed by a rheumatologist (64 %, *n*=16) or geneticist (44 %, *n*=11), citing hypermobility (72 %, *n*=18), skin findings (64 %, *n*=16), and pain (44 %, *n*=11) as critical to making a diagnosis of EDS. Diagnoses prior to a diagnosis of EDS included depression/anxiety (72 %, *n*=18), acute abdominal pain (60 %, *n*=15), and fibromyalgia (60 %, *n*=15). Participants reported the reasons for seeking medical care included orthopedic issues (80 %, *n*=20) and gastrointestinal problems (52 %, *n*=13). The manifestations participants sought medical care for were not part of the current diagnostic criteria for EDS (hyermobility, skin extensibility and fragility), resulting in diagnostic delays.

The Relationship Between Delayed Diagnosis and Quality of Life in Individuals with Fabry Disease

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Fabry disease (FD) is a rare progressive genetic disorder marked by a wide range of variably expressed clinical features including initial symptoms of debilitating neuropathic pain, chronic fatigue, anhidrosis, extreme temperature intolerance, gastrointestinal problems and angiokeratomas (benign skin lesions). Cardiac disease, renal impairment, and cerebrovascular accidents typically emerge later in the course of the disease and may lead to early mortality in the 4th or 5th decade of life. Fabry disease often falls outside the scope of most physicians' knowledge, with symptoms ranging across many areas of medical specialization and overlapping with other disorders. Patients are commonly misdiagnosed, have their pain attributed to psychosomatic causes and spend years with uncertainty about their medical condition before an accurate diagnosis is made. A delay in diagnosis prevents appropriate treatment, specifically the initiation of enzyme replacement therapy, which can improve pain and overall prognosis, yet is more effective when initiated earlier in the course of FD. This study proposed that the length of diagnostic delay was inversely correlated with health-related quality of life (HRQOL). A survey consisting of FD-specific questions and the Medical Outcomes Study SF-36 questionnaire to assess HRQOL was distributed by email to members of the National Fabry Disease Foundation and the Fabry Support and Information Group. Respondents included 164 individuals, of which 45 were males, 118 were females and 1 without gender specified. Results confirmed the relationship between longer diagnostic delay and lower HRQOL. Furthermore, the mean diagnostic delay was 19.8 years, which is more than 6 years longer than previous research suggests. The long diagnostic delay, reduced quality of life and the potential for adverse consequences in undiagnosed and untreated FD patients highlight the need for increased physician awareness to enable earlier diagnosis and may also be relevant to newborn screening initiatives for FD.

An Exploration of the Approach to Family Planning Among Adult Siblings of Individuals with Undiagnosed Conditions

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The current study's goal was to gain a general knowledge on the factors that impact the approach adult siblings of individuals with an undiagnosed genetic condition take when planning a family. Reviewing past studies on family planning or siblings of individuals with disabilities, we identified two gaps in the literature. First, adult's knowledge for what their sibling's condition meant for their reproduction was not clearly communicated to them in childhood and second, sibling life experiences were typically evaluated in childhood. The study explored the factors involved in the decision-making process in the context of an unknown recurrence risk. The study population was identified via the NSGC email list-serve and snowball recruitment. Potential participants were screened and five eligible respondents were interviewed by phone. A semi-structured interview guide was used; 15 standard questions were asked to each participant and unique questions were asked when clarification was needed. The interviews were recorded and transcribed. Salient themes were uncovered using modified-grounded theory after the transcripts were hand-coded by the Principal Investigator. Themes included topics on information and control, reflections on the participants' life experiences, and social support. Modifying factors in the decision-making process included age, finances, timing constraints, and caretaker expectations. Participants reported evaluating different family planning possibilities such as adoption, biological children, egg donor/surrogacy, and no children. All participants conveyed that current decisions were subject to change. This exploration established that the decision-making process is flexible and that the uncertainty in recurrence risk and adult siblings' future caretaker status may play major roles in the decisions individuals make when planning a family. The research indicated that genetic counselors can be a source of balanced information and can provide guidance, acceptance, and support throughout the decision-making process.

Absence of Genotype-Phenotype Correlations in *RPE65*: Implication for Identification of Patients Suitable for Gene Therapy

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In many inherited disorders, genotype-phenotype correlations provide insight into onset of disease, rate of progression, and degree of severity. Both Leber congenital amaurosis type 2 (LCA2) and autosomal recessive retinitis pigmentosa (RP) type 20 (RP20) are caused by mutations in the RPE65 gene. We performed a retrospective chart review of patients with known *RPE65* mutations to determine the spectrum of clinical diagnoses associated with this gene. We also examined the *RPE65* mutations identified in individuals enrolled in the phase 1/2 and phase 3 *RPE65* gene therapy clinical trials at The Children's Hospital of Philadelphia, and compared those with *RPE65* mutations reported in the literature. Over 125 discrete mutations were identified in the RPE65 gene in individuals with inherited retinal disease. These include missense and nonsense point mutations, frameshift mutations resulting from small insertions and deletions, and splice site mutations. Patient diagnoses included LCA2, early onset retinal dystrophy (EORD), and RP20. Missense, nonsense, splice site, and frameshift mutations were described in patients across all diagnosis groups. In the cohort of subjects reviewed in this study, no clear genotype-phenotype correlations emerged. The distinction between RP20, LCA2, and other clinical diagnoses given to those with autosomal recessive *RPE65* mutations appears to be based primarily on clinical symptoms and age of onset, and unrelated to underlying genotype. These data have important implications for the identification of patients suitable for *RPE65* gene replacement therapy, and suggest that *RPE65* should be considered in not only patients with LCA, but also early onset severe forms of retinal dystrophy and autosomal recessive RP.

The Diagnostic Odyssey in the Young Adult Population: A Case Perspective of Desminopathy

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We present the case of a 27 year old woman who came to genetics after several years of a diagnostic journey involving multiple specialists and invasive procedures. She was developmentally on target and a well-trained athlete before onset of symptoms approximately 7 years ago. Initial symptoms included gradual onset fatigue that was attributed to life style changes. Hypothyroidism was diagnosed and treated, however symptoms persisted. At the age of 23 she had a syncopal episode and was found to have cardiac arrhythmia with complete heart block. She now has class III congestive heart failure with cardiomegaly and ventricular dysfunction. A unifying diagnosis was not apparent initially, and she had multispecialty evaluation over the next several years, including skeletal muscle biopsy. Muscle histology suggested possible metabolic myopathy with non-specific histology. An inflammatory myopathy could not be excluded, and glycogen storage disease was also considered due to presence of glycogen deposition in muscle. Genetics work up included metabolic screening and molecular testing for cardiomyopathy. This patient was shown to have a heterozygous c.1216C>T mutation in the DES gene, consistent with an autosomal dominant myofibrillar myopathy. *DES* codes for the protein desmin, which is important for maintaining the structures of sarcomeres in skeletal and cardiac muscle. Myofibrillar myopathy is a muscular dystrophy with variable features, including progressive weakness and cardiomyopathy. This case illustrates the importance of establishing an accurate genetic diagnosis for at least two reasons. Due to progressive skeletal and cardiac disease, establishing a definitive diagnosis was urgent as this patient was being considered for a cardiac transplant. Secondly, after several years, this young woman can move toward knowledge and acceptance of her life-limiting diagnosis.

Increasing Diagnosis and Treatment in Hereditary Angioedema

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1. InformedDNA

Hereditary angioedema (HAE) is a rare, life-threatening and frequently disabling disease characterized by episodic subcutaneous and submucosal swelling. HAE is an autosomal dominant condition with significant clinical variability. Over the last 10 years, several new treatments have been approved for the treatment of HAE, improving the prognosis of individuals affected with this condition. Consensus guidelines support early and accurate diagnosis to reduce disease morbidity and mortality, but significant barriers reduce effective diagnosis in this patient community. We initiated a program to provide subspecialty level genetic counseling to patients and family members in the HAE community. Patients were given the choice of telephone-based, video/Web-based, or in-person genetic counseling appointments; the overwhelming majority chose telephone-based services. Over 200 individuals registered for the program; 69 % followed through with appointments. On average, each unrelated proband reported a family history in which 7 at-risk relatives were identified. Although the genetic counselor offered to provide follow-up counseling sessions to those individuals, few at-risk family members made genetic counseling appointments. We sought to understand the barriers to family outreach, and provide meaningful solutions. Reported reasons for not reaching out to family include uncertainty in personal diagnosis, stigma attached to HAE diagnosis, and lack of confidence in answering family members' questions. To help address these issues, we provide family outreach letters, physician support, and social media outreach. We developed a Facebook page with updates about diagnosis, inheritance, disease management, and support. To date, more than 325 individuals follow the Facebook page. Utilization of telephone genetic counseling services has the potential to significantly increase diagnosis and quality of care for patients and at risk family members in the HAE community. Patient satisfaction data, collected anonymously, has supported the success of this program.

Knowledge and Patient Satisfaction Following Genetic Counseling for Patients with Inherited Retinal Dystrophy

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Introduction: Few studies have characterized the baseline knowledge of patients with Inherited Retinal Dystrophies (IRD) and none have directly addressed the impact of genetic counseling on patient understanding in this population. This study assessed the baseline knowledge of patients receiving specialized ophthalmic genetic counseling and evaluated the impact of counseling on their understanding of IRD genetics as well as patient satisfaction. Methods: Adults with IRD or parents of pediatric patients (n=10) seen at the Cole Eye Institute were surveyed. Prior to genetic counseling, participants met with the researcher, and were read a baseline questionnaire which included IRD-related knowledge questions and beliefs about the etiology of their condition. Two weeks after the counseling session, participants completed a post-counseling telephone survey which included the same knowledge items as the pre-counseling survey in addition to the Genetic Counseling Satisfaction Survey. The impact of genetic counseling, prior beliefs about the etiology of their visual impairment, and demographic factors on knowledge scores were assessed. Results: Nine participants completed all parts of the study. Patients demonstrated significant increases in IRD-related genetics knowledge 2 weeks after genetic counseling (78.1 % correct) compared to baseline knowledge scores (48.6 % correct, p<.001). Participants who had previously attributed their IRD to non-genetic causes demonstrated lower baseline knowledge scores compared to those who endorsed a genetic cause (37.5 % vs. 57.2 %, p=.077). All patients reported high levels of satisfaction with genetic counseling (avg 4.67/5). Conclusions: These results suggest that genetic counseling improves knowledge for patients with IRD and that patients are highly satisfied with these services. This IRD knowledge survey may be a useful clinical and research tool for assessing patient understanding provided during counseling for IRD and potentially promote patient satisfaction with the genetic counseling process.

III. Adult/Cardiology

Genetic Testing Experience in a Large Cardiovascular Genetics Referral Program

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Background: We performed a retrospective review of cardiac genetic testing performed at a large cardiovascular genetics referral center in Chicago, IL where clinical gene testing has been performed with an experienced genetic counselor since 2004. This period encompassed the growth in gene panel testing for cardiovascular disease. Methods: Cardiac gene testing performed between 2004 and 2015 was queried within a Progeny database and retrospectively analyzed. Clinical diagnosis of hypertrophic (HCM), dilated (DCM) and arrhythmogenic right ventricular (ARVC) cardiomyopathy were delineated. Patient populations with

significant arrhythmia burden of unknown origin and sudden cardiac arrest were analyzed individually. In all cases, pathogenic mutations as reported by the clinical lab were counted excluding variants of uncertain significance. Results: Detection rates for pathogenic mutations were: HCM 33.9 % (21 individuals with mutations (+); *n*=62); DCM 31.9 % (37+; *n*=116); and ARVC 18.2 % (2+; *n*=11). In DCM, panels of 18 or fewer genes yielded a detection rate of 28.6 % (18+; *n*=63); an LMNA only gene test accounted for 13 of the 18+ (38.2 %). DCM panels over 18 genes yielded a detection rate of 34.0 % (18+; *n*=53). Addition of the titin (*TTN*) gene into cardiomyopathy panels in 2012, the pathogenic mutation detection rate prior to *TTN* was 31.7 % (26+; *n*=82) versus after TTN was 32.4 % (11+; *n*=34). Gene testing of those with significant arrhythmia burden (without sudden cardiac arrest or LongQT diagnosis, *n*=9) yielded a pathogenic mutation in 1 (11.1 %). Aborted sudden cardiac arrest since 2009 (*n*=12) tested by large gene panels (typically over 50 cardiomyopathy and arrhythmia genes) yielded a pathogenic mutation in 2 (16.6 %). Conclusions: DCM gene testing has yielded pathogenic mutation detection rates of 32 %. Cardiac genetic testing in those with significant arrhythmia burden of unknown etiology and aborted sudden cardiac arrest have comparatively lower yield despite larger gene testing panels. Gene testing is essential to better assess arrhythmia risk for surviving family members.

Diagnostic Exome Sequencing with Inheritance Model-Based Analysis: Results from a Cohort of 81 Probands Referred with Cardiac Indications as Compared to the Group of 500 Unselected Families with Undiagnosed Genetic Conditions

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Purpose: Diagnostic exome sequencing has been shown to have definite utility in cases of undiagnosed genetic conditions. This paper presents data from 81 referrals with a cardiac indication, as compared to the entire population of 500 unselected referrals. Methods: Family-based exome sequencing included whole-exome sequencing followed by family inheritance-based model filtering, comprehensive medical review, family co-segregation analysis, and analysis of novel genes. Comparisons in diagnostic exome sequencing results were made between the population of 419 unselected families with undiagnosed genetic conditions without a cardiac indication and the cohort of 81 patients referred with a cardiac indication in addition to the other indications for referral. Results: Referrals made with a cardiac indication comprised 16.2 % (81/500) of the total referrals. All referrals made for patients with a cardiac indication also included at least one other indication for referral. A positive or likely positive result in a characterized gene was identified in 23.5 % (19/81) of patients with a cardiac indication. This rate is not significantly different from the group of referrals made without a cardiac indication 133/419 (31.7 %) (p= 0.1378). A novel gene finding was identified in 4.3 % of patients (3/70) which is not statistically different from the 8.1 % (28/346) in patients with a novel finding in the non-cardio group. The novel findings within the cardiac indication cohort all occurred in genes associated with cell adhesion protein production. Conclusion: Overall, this paper presents results from a large clinical cohort of diagnostic exome sequencing. These data demonstrate similarities between individuals referred for exome sequencing with and without a cardiac indication. This paper illustrates a number of interesting findings in the types of genes discovered within the population of exome sequencing patients. The results suggest opportunity for follow-up in the population of patients presenting with a cardiac indication within the spectrum of an undiagnosed genetic condition.

Pulmonary Arterial Hypertension: Specialists' Knowledge, Practices, and Attitudes of Genetic Testing and Genetic Counseling

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Background: Pulmonary Arterial Hypertension (PAH) is a disease that is characterized by obstruction of pre-capillary pulmonary arteries which leads to sustained elevation of pulmonary arterial pressure. Early interventions can help to mitigate the disease course if those at risk are identified through methods such as genetic testing. Current practice guidelines from the American College of Chest Physicians in addition to other literature have been in existence for more than 10 years and recommend genetic counseling and offering genetic testing to individuals with heritable PAH, idiopathic PAH, and their family members. However, it is unclear if PAH specialists follow these recommendations. Thus, the objective of this research was to determine the knowledge, utilization, and perceptions about genetic counseling and genetic testing of PAH specialists. Methods: A survey was custom designed and distributed to PAH specialists' in order to assess their knowledge, practices, and attitudes about the genetics of PAH. Parametric and non-parametric statistics were used to analyze responses with comparisons of groups performed using the Wilcoxon rank sum test. Results: PAH specialists had low perceived and actual knowledge of the genetics of PAH with 13.2 % perceiving themselves as knowledgeable and 27 % actually being knowledgeable. Although these specialists have positive or ambivalent attitudes about genetic testing and genetic counseling, they have poor utilization of these genetic services with almost 80 % of participants never or rarely ordering genetic testing or referring their patients with PAH to a genetic counselor. Physicians, who would be the primary specialist to utilize these genetic services, have both lower utilization of and perceptions of the value of genetic testing and genetic counseling compared to non-physicians (p=<0.05). Conclusion: Taken together our results suggest that increased education and awareness is needed about the genetics of PAH as well as the benefits of genetic testing and genetic counseling for individuals who treat patients with PAH.

MicroRNAs as a Marker of Cardiovascular Disease in Marfan Syndrome and Marfan-Related Disorders

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Introduction: Marfan syndrome affects many body systems, but aortopathy is the most common cause of death, and predicting the cardiovascular complications in any given individual remains difficult. In several diseases, micro RNAs (miRNAs) have emerged as a promising biomarker to indicate the presence of pathology. This study explores the use of miRNAs as biomarkers in predicting onset and severity of aortopathy for patients with Marfan syndrome and Marfan-related disorders. Hypothesis: The hypothesis was that circulating miRNA profiles are unique in individuals with Marfan syndrome as compared to controls. A secondary aim of the study was to determine whether unique miRNA profiles will aid in identifying those at high risk for aortic aneurysm. Methods: Subjects were recruited with a clinical diagnosis of Marfan syndrome. The subject's demographic information, diagnosis, skeletal features and aortic measurements were also documented. An array for 754 miRNAs and real time polymerase chain reaction confirmation of select miRNAs were performed. Results: Nine subjects were enrolled (7/9 subjects with

Marfan syndrome and 2/9 with Loeys-Dietz Syndrome). Two miRNAs were up-regulate (miR-298 and miR-342) and twenty-nine were miRNAs were down-regulated in subjects with Marfan syndrome or Marfan-related disorders. Conclusions: This study provides preliminary evidence that circulating miRNA profiles are distinct in patients with Marfan syndrome. This provides further evidence for the utility of miRNAs as a biomarker for aortopathy in Marfan syndrome. Further studies are needed to investigate whether miRNAs can differentiate between patients with high risk and low risk of developing aortic disease progression. Uncertainty surrounding the prognosis of aortopathy in Marfan syndrome raises the question of whether a personalized risk assessment using miRNAs would benefit the family and could be incorporated into the genetic counseling process.

Familial Hypercholesterolemia: Characterization of a Pediatric Population and Evaluation of Parental Knowledge and Attitudes

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Familial hypercholesterolemia (FH) is a dominant condition estimated to affect 1 in 500 individuals. If untreated, FH leads to premature coronary heart disease and death. Despite the high prevalence, screening guidelines, and effective treatment, FH remains underdiagnosed and undertreated. Current guidelines recommend universal cholesterol screening in adolescence and genetic testing for individuals with suspected FH. We sought to identify the prevalence of FH at a pediatric medical center and to characterize the population with a retrospective chart review. A survey was used to assess parental beliefs and attitudes towards genetic counseling and testing and to assess knowledge of FH. The prevalence of FH was calculated as the proportion of children who have FH compared to all individuals seen at the institution. A mean knowledge score was reported and analyzed using a Wilcoxon test. The prevalence of FH was 4/10,000 with only 1 % of individuals between the ages of 9 and 11 receiving cholesterol screening. Of the 180 individuals with suspected FH, 28 (16 %) had been prescribed a statin and none had received genetic counseling or testing for FH. The survey response rate was 44 %. Forty-eight (63 %) respondents reported interest in genetic counseling about FH and 42 (55 %) reported they had never discussed FH with relatives. Mean knowledge scores trended higher among participants who reported speaking about FH with a healthcare provider (p=0.061). To our knowledge, this is the first prevalence estimate for FH in a pediatric medical center and demonstrates suboptimal diagnosis and adherence to cholesterol screening and genetic testing guidelines. Results suggest that families are interested in genetic counseling for FH and that less than half of families discuss FH with relatives. Genetic counseling has previously been associated with increased disease knowledge, family communication and heightened adherence to recommendations for at risk family members. Research regarding barriers to cholesterol screening and the impact of genetic counseling and testing on FH is needed.

Patient Recall, Interpretation and Perspective Regarding an Inconclusive Result in Long QT Syndrome Genetic Testing

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Introduction: Patients' perceptions of inconclusive genetic testing results have been investigated in the cancer setting, however little to no data are available on patient perspectives to these results in inherited heart disease. We explored how receiving an inconclusive result can affect patient recall, perception and interpretation. As well, we studied a possible relationship between their personal circumstances and recall accuracy. We report qualitative results of 16 telephone interviews with individuals who received a negative or variant of unknown significance (VUS) result from Long QT syndrome (LQTS) testing between 2008 and 2013. Methods: Semi-structured telephone interviews were conducted with individuals with an inconclusive LQTS result. Analysis of interviews was conducted through grounded theory by two coders. Results: The type of genetic testing result does not affect patient recall. When receiving a negative result, a large proportion of participants perceived no change in the outlook on their diagnosis, while the perception of influence on family was varied. A proportion of participants felt relief, perceiving that their families were no longer at risk. Conversely, majority of participants felt they maintained an awareness of their condition after the result disclosure. Many participants found they consulted a results letter following the appointment as a source of information, and the language used by participants reflected that of the patient letters. Some participants noted a need for more tailored information. Conclusions: This study demonstrates that a negative result suggests to some patients a non-genetic etiology to their diagnosis. As well, the reasoning for testing and understanding of their result informed three main reactions of disappointment, relief or questioning their diagnosis. These findings highlight the importance of a patient letter as an educational tool. This study also highlights the need for tailoring counseling sessions to individual patient needs and situation and explicitly addressing topics of confusion for patients.

Preimplantation Genetic Dianosis in Familial Dilated Cardiomyopathy: Potential Limitations and the Continued Role of Medical Genetics

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Introduction: Familial dilated cardiomyopathy (DCM) is a genetically heterogeneous cardiac disorder, most commonly with autosomal dominant transmission. Current genetic testing panels analyze up to about 50 genes; however, disease causing mutations are identified in only 25–40 % of families with DCM, arguing that the genetics of this disorder are still not fully understood. Preimplantation genetic diagnosis (PGD) technology allows for individuals with certain genetic disorders to undergo *in vitro* fertilization (IVF), with implantation of embryos that do not harbor the familial mutation, and genetic counseling should be an important component of this process. Case Report: A 5 month old girl was diagnosed with heart failure necessitating cardiac transplant at 9 months; her paternal half-brother was then diagnosed with DCM at 5 months and required transplant at 8 months. Their father had a history of cardiomyopathy diagnosed at age 18. Genetic testing identified presumed pathogenic *MYH7* mutation and variant of unknown significance (VUS) in *MYBPC3* in both affected children in 2009. In 2013, the family returned to genetics after having undergone IVF with PGD, resulting in monozygotic male twins. Genetic counseling was not pursued during IVF. Echocardiogram at 3 months identified left ventricle dysfunction in both twins, and LV trabeculations in one. Genetic testing confirmed neither *MYH7* nor *MYBPC3* variant was present. In the interim, the *MYH7* mutation had been reclassified to a VUS. Neither of the affected twins has required cardiac transplantation, but continue to be closely followed and treated

for cardiomyopathy. The family has not yet elected to pursue additional clinical or research testing. Discussion: Dilated cardiomyopathy is a complex genetic disorder, and the limitations of clinical testing can make genetic counseling difficult even in families with known or suspected mutations. This case identifies the challenge of utilization of PGD for DCM, and also highlights the importance of continued involvement of medical genetics in patient care.

Goal Achievement in Young Adults with Asperger Syndrome and High Functioning Autism

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Purpose: This study aimed to evaluate perspectives of young adults with Asperger syndrome (AS) and high functioning autism (HFA) regarding supports, services, future goals, and confidence in their success. The goal was to identify valuable supports and areas in which this support was lacking. Identifying areas of support for AS/HFA young adults transitioning to adulthood aids in providing services for successful goal achievement. The study has value among genetic counselors as under covering genetic etiologies of autism has led to referral of families with ASD to genetic clinics. Methods: AS/HFA young adults were invited to participate via online questionnaire, telephone or in-person interview. Email invitation letters were sent to local and national support groups and colleges in South Carolina, and on social media sites. The questionnaire and interviews included questions regarding receiving a diagnosis, education, supports, services, future goals, feelings towards the DSM-5, and demographics. Results: Of the total respondents, (N=12), eight met inclusion criteria; four completed online questionnaires, two completed telephone interviews, and two completed in-person interviews. Participants felt their diagnoses provided a self-identity and explanation for differences. A family member, teacher, or peer who understood the diagnosis or was similar to the participant was the greatest source of support. Current services were minimal, and participants lacked confidence in achieving future goals, feeing they would benefit from help in social skills or goal planning. Participants did not favor the new DSM-5 change due to their identification with the diagnosis. No participants reported meeting with a genetic counselor. Conclusions: AS/HFA young adults are lacking in support during the transition to adulthood and pursuit of future goals, particularly in the area of social communication. The findings of this study allow genetic counselors to be better prepared in identifying the areas of need and directing families to appropriate resources when they present in clinic.

Psychological Effects of a Positive Test Result in a Cardiomyopathy Gene: A Comparison of Symptomatic and Asymptomatic Mutation Carriers

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The psychological implications of genetic testing have been well studied in populations such as *BRCA1* and *BRCA2* mutation carriers, presymptomatic Huntington disease carriers and *APOE* mutation carriers. However, genetic testing for cardiac disease is a new and growing area and, as such, the psychological implications of testing in this population are not well understood. Using a subpopulation of the Columbia University Medical Center's study regarding psychological implications of cardiogenetic testing, this study assessed how a positive gene test result in a cardiomyopathy gene affects psychological well-being. This study reviewed and compared the psychological effects of genetic test results for 46 symptomatic and asymptomatic mutation carriers for hypertrophic cardiomyopathy and dilated cardiomyopathy using a unique survey, which included an adapted Multidimensional Impact of Cancer Risk Assessment (MICRA) scale for cardiac disease, Impact of Events scale and Satisfaction with Decisions scale. This study found most positive mutation carriers of a cardiomyopathy gene to be satisfied with their decision to pursue genetic testing and felt informed about the process. However, the symptomatic subset of the study population reported significantly higher levels of distress and avoidance tendencies due to their positive genetic test results. This could be due to the combination of the physical manifestation of the disease and the implications of a mutation in a cardiomyopathy gene. A significant portion of the population also reported their positive genetic test results to affect lifestyle and family decisions, such as having children, changing careers and purchasing life insurance. This shows the importance of pre- and post-test counseling to address the psychological impact of genetic testing. Genetic counselors need to address these issues to ensure patients understand the implications and should be customized based on the medical status of the patient.

Moving Beyond the 1 %: Incorporating the Exome Aggregation Consortium Data into Variant Interpretation and Classification

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1. Invitae

The availability of population frequency data on sequence variants has increased exponentially over the past decade. The Broad Institute recently released the Exome Aggregation Consortium (ExAC) database, which includes sequence data of more than 60,000 individuals from various studies. In this study, we review the interpretation of variants of uncertain significance in genes associated with hypertrophic cardiomyopathy (HCM), which had conflicting clinical and population data. Specifically, p.Arg495Gln and p.Val28Met in the MYBPC3 gene were reanalyzed using the ExAC data. The p.Arg495Gln variant has been reported in multiple cases of HCM, as have other changes affecting this residue, arguing towards pathogenicity. However, this variant also had been reported to have a population frequency of 0.17 % (1/569 European alleles, dbSNP), suggesting p.Arg495Gln may be benign since it approaches the incidence of HCM. This conflict is resolved in the ExAC data, where the frequency is 0.0015 % (1/67,000 European alleles). p.Arg495Gln is now reclassified as pathogenic. The p.Val28Met variant in the MYBPC3 gene had been reported in an individual with suspected HCM and was absent from control and population databases, evidence which suggest pathogenicity. However, p.Val28Met is present in ExAC in 14/12,646 (0.1 %) alleles from a South Asian subpopulation, and one homozygote is also present. As a result, p.Val28Met is now reclassified as likely benign. The reclassification of these variants emphasizes the benefit of large population variant databases. Smaller databases provide insufficient power for confidence in low frequency variants and have the potential for misinterpretation. ExAC is a powerful tool as its large sampling minimizes the effect of sampling bias. Variants present at frequencies less than 1 %, a historical threshold for benign classifications, in a large dataset may now be classified as benign in genes associated with autosomal dominant conditions. In conclusion, larger population variant databases significantly improve the accuracy of variant classification.

IV. Cancer

End of Life Discussions: Exploring How to Talk About Hereditary Cancer at the End of Life

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The discussion of hereditary cancer can be difficult to understand and cope with emotionally. In order to best provide family members of terminally ill cancer patients the information about hereditary cancer risk, it is important to assess how receptive the population is to the information, as well as to identify the best method of delivery. Therefore, the aims of the study were, 1.) to identify potentially effective and appropriate methods of delivery of cancer genetic information to family members of patients with terminal cancer, and 2.) to assess the impact that the exploration of hereditary risk of cancer has on the family members of the dying patients. This was a descriptive qualitative study using phenomenological approach. Audiotaped semi-structured interviews were conducted with seven blood relatives of patients diagnosed with terminal cancer and admitted to an inpatient palliative care unit at an academic medical center. Participants included six females and one male. Their relationship to the patient was sibling, child, aunt or mother. The audiotapes were transcribed verbatim and loaded into Atlas.ti for analysis. Common emerging themes were verified prior to dissemination. Participants expressed opinions about open communication with health care professionals, as well as communication among family members. Participants indicated preferred methods of communication with health care professionals, including written, in person, and electronic/telephone communication. Emotional responses regarding the topic of hereditary risk discussion in this population, and feelings about obtaining genetic information were revealed. Emotions expressed included apprehension, reluctance, worry, hostility and stress. Overall, this study suggested that open communication is an important aspect of a hereditary cancer risk discussion, and the best method of delivery is situational; however, this needs to be explored further. Due to the wide range of emotions, it is important to be cognizant of these emotions and adapt the discussion of hereditary cancer appropriately.

The Impact of a Clinic-Based Pancreatic Cancer Research Registry in Identifying Actionable Germline Mutations

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Approximately 10 % of pancreatic cancer is estimated to be hereditary. Despite the recognized hereditary fraction of pancreatic cancer, we hypothesized that individuals affected with pancreatic cancer or with family histories of pancreatic cancer are under-referred for genetic assessments. In this study we evaluated the value of a clinic-based research registry in identifying actionable germline mutations. Through Quebec Pancreas Cancer Study (QPCS), a clinic-based research registry, 278 individuals were evaluated between April 2012 and April 2015 by a genetic counselor for hereditary risk. We identified 154 individuals with potential risk for genetic predisposition based on family histories, young-onset of disease, multiple primary cancers, ancestries with recurrent predisposing gene mutations, and chemotherapeutic responses suggestive of an underlying DNA repair gene mutation. Of these cases, 16 were referred to QPCS by clinical genetics. 9 of these cases had been found to carry germline predisposing variants and 7 had negative genetic testing results. These cases were referred to QPCS for pancreatic cancer screening, penetrance, and gene discovery studies. An additional 11 cases referred to QPCS independently of clinical genetics (i.e., by surgical or medical oncology for a pancreatic lesion) were found to have had a previous clinical genetics assessment, of which 4 individuals were found to be carriers of known predisposition genes. These genetic assessments may have been missed in routine surgical or medical oncology consultations. The remaining 127 cases considered at increased risk for pancreatic cancer predisposition had not undergone prior genetic evaluations. These individuals were counseled and underwent genetic testing on a QPCS research platform, including recurrent mutation testing and next generation sequencing. Even though testing was limited to opportunities available through the QPCS research initiatives, we identified actionable *BRCA2* and *PALB2* mutations in 7/127 individuals (5.5 %).

The Ever Changing Role of Genetic Counseling in Oncology

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In the world of genetics, nothing is static. The question is: are best practices being developed to keep stride? Somatic tumor testing is becoming a routine aspect of oncology care and genetic counselors have the potential to play an important role in the education and counseling of patients and providers. We compare and contrast two cases that involved tumor testing and genetic counseling, with differences in pre-test counseling and outcomes. Case One: 57-year old male with metastatic colon cancer, initially referred for genetic counseling for his personal and family history. At the initial session, the family met National Comprehensive Cancer Network Guidelines for BRCA genetic testing based on multiple individuals with early onset breast cancer. Tumor testing was discussed, as well as BRCA testing for an affected relative. Tumor testing revealed a BRCA2 mutation that had previously been reported as a germline mutation. Follow up counseling ensued and this patient underwent germline testing for the same BRCA2 mutation, which confirmed a diagnosis of hereditary breast and ovarian cancer in this family. The family was appropriately prepared for the outcome because of appropriate pre-test counseling. Case Two: 57-year old female with metastatic colon cancer. Genetic counseling occurred after tumor testing revealed somatic *APC* and *TGFBR2* mutations. The oncologist misinformed the patient that the findings were likely hereditary. She was anxious and expected germline testing despite a negative family history. The genetic counselor explained that the personal and family history was not consistent with a hereditary cancer syndrome. Nevertheless, the patient requested targeted germline testing, which was negative. She was relieved not have a hereditary cancer syndrome, but was upset about the unnecessary anxiety created by her oncologist's remarks. Genetic counselors play an important but challenging role in the setting of somatic testing. This is a potential area for consideration of development of best practices for genetic counselors.

Assessing Documentation of Cancer Family History in the Pediatric Oncology Setting

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Background: Well described adult cancer predisposition syndromes, such as hereditary breast and ovarian cancer syndrome, have illustrated the importance of obtaining family history (FH) in comprehensive oncology care. Given the rare nature of pediatric cancer predisposition syndromes and their associated cancers, it is unclear how often FH details are recorded in the pediatric oncology setting. We report findings of a FH survey analysis and medical chart review of 182 pediatric oncology patients enrolled in the BASIC3 clinical trial. Methods: The National Human Genome Research Institute/National Cancer Institute-funded BASIC3 trial examines the clinical utility of tumor and germline whole exome sequencing (WES) in the care of childhood cancer patients at the time of solid tumor diagnosis. Upon enrollment, participant families are asked to complete FH surveys, which include targeted FH cancer questions. Study genetic counselors review surveys and the patient's electronic medical record (EMR) for personal and family medical history and report relevant findings to the WES laboratory. FH details may also be reported by the family at the results disclosure. Results: Of 182 families, 60 (33 %) had at least one parent complete the FH survey. Of this group, 33 (55 %) of patients had missing FH details in the EMR, including three to four generations of family members with cancer diagnoses or the age of cancer diagnosis. There were germline diagnostic WES results in 16 patients relevant to their tumor diagnosis, and 56 % (9) had relevant FH details that were not noted by their provider. Conclusions: FH information necessary for genetic cancer risk assessment, referral for genetic evaluation, and determination of the need for genetic testing is not reliably recorded in the medical record of pediatric oncology patients. Improved FH assessment is needed to provide optimal genetic evaluation in this population.

A Population-Based Sample of Breast Cancer Survivors Who Accessed BRCA Testing Recalled Greater Adherence to Cancer Genetic Counseling Practice Guidelines when a Genetic Healthcare Provider was Involved

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Background: Although any physician may order BRCA testing, many professional organizations endorse genetic counseling (GC) prior to genetic testing (GT). Differences in GC services delivered by board-certified genetic healthcare providers (GHP) versus non-genetic healthcare providers (non-GHP) have been identified in a high-risk cohort of BRCA carriers, but it is important to confirm this in a population-based sample. Methods: Women diagnosed with invasive breast cancer <= age 50 in 2009–2012 were recruited through the Florida cancer registry. Participants completed a baseline questionnaire and provided BRCA test reports. Summary statistics and chi-square tests were used for analysis. Results: Of 495 women who reported having GT prior to enrollment, 153 (31 %) had returned their test report at the time of analysis. Of these 153, 84 % were white and 10 % were BRCA carriers. Those without GHP involvement (n=123) did not differ significantly from those with GHP involvement (n=30) by sociodemographic factors. Although having a pretest discussion was high in both GHP and non-GHP subgroups, those with GHP involvement were significantly more likely to report adherence to 6 of 8 recognized elements of GC. Compared to the non-GHP subgroup, those with GHP involvement more often recalled: (1) having a pedigree collected (85 % vs. 51 %; p=0.005); (2) receiving a summary letter (60 % vs. 22 %; p<0.001); (3) discussing other hereditary cancer syndromes (45 % vs.15 %; p=0.003); (4) discussing uninformative test results (95 % vs. 74 %; p=0.04); (5) discussing risks to life and disability insurance (35 % vs. 8 %; p=0.002) (6) discussing laws that protect against genetic discrimination (65 % vs. 17 %; p<0.001); and (7) that their doctor encouraged them to share their test results with relatives (73 % versus 58 %; p=0.1). Conclusions: Our results suggest that GHP involvement was associated with increased patient recall of adherence to nationally recognized cancer GC practice guidelines. Future studies should assess if these differences influence whether women share GT results with at risk relatives.

Personal and Family Cancer History in Li-Fraumeni Syndrome Diagnosed on Multi-Gene Testing

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Introduction: The emergence of next-generation sequencing with multi-gene testing has led to unexpected *TP53* results in families who may not meet recognized clinical criteria for Li-Fraumeni Syndrome (LFS) over a one year period. Methods: A chart review was performed to determine personal and family history characteristics of patients who tested positive for a deleterious *TP53* mutation on pan-cancer (broad spectrum) multi-gene testing for twenty five or more genes. Results: Between April 1, 2014–March 31, 2015, 441 patients received results from pan-cancer multi-gene testing. Five patients tested positive for a deleterious *TP53* mutation of whom: 1) four did not meet recognized clinical diagnostic criteria (classic or Chompret) for a diagnosis of LFS at the time of testing; and 2) three met National Comprehensive Cancer Network (NCCN) clinical testing guidelines for LFS. Two patients did not meet clinical diagnostic criteria or NCCN clinical testing guidelines. Discussion: This series highlights the high variability in expressivity of what is historically considered a highly penetrant inherited cancer syndrome. Given the majority of our families did not meet clinical diagnostic criteria for LFS, it is clear that multi-gene testing is leading to widening of the disease phenotype. Identification of families who do not meet clinical diagnostic criteria presents many unanswered questions such as the existence of genotype/phenotype correlations, the presence of genetic or environmental modifiers, and the refinement of quantifying cancer risks (particularly given that cancer risk estimates are based on the classic highly penetrant families). Consequently, this series emphasizes the need to more broadly assess genotype/phenotype correlations, cancer risks, risk modifiers, and ultimately be able to advise these patients about cancer risk management.

Characteristics of Li-Fraumeni Syndrome in a *CHEK2* Multi-Gene Panel Cohort

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Pathogenic mutations in *CHEK2* have been implicated in some *TP53*-negative patients with Li-Fraumeni Syndrome (LFS) cancer histories. Literature is conflicting regarding LFS phenotype of *CHEK2*+ patients. With the use of multi-gene panel testing, *CHEK2* is investigated in this population more frequently. The purpose of this study was to describe LFS characteristics amongst *CHEK2* mutation carriers (*CHEK2*+). Clinical histories of 594 patients who underwent panel testing between 3/2012 and 12/2014 and harbored pathogenic/likely pathogenic *CHEK2* mutations were queried. Where personal and family cancer history (hx) were available, the cohort was analyzed for TP53 testing criteria met including classic LFS, Chompret, and breast cancer <36 criteria per National Comprehensive Cancer Network guidelines (v1.2015). The cohort was analyzed to determine who met LFS-like (LFL) criteria (Birch or Eeles). The prevalence of LFS cancers including breast (BR), sarcoma (SAR), adrenocortical carcinoma (ACC) and others was also reviewed. *CHEK2*

mutations were identified in 594/23555 patients (2.5 %). Patients with biallelic mutations in *CHEK2* (*n*=7), or with additional mutations in genes other than *CHEK2* (*n*=52) were excluded from analysis. No *CHEK2*+ patients met criteria for classic LFS; 30/464 (6.5 %) met Chompret; 3/468 (0.6 %) met Birch; and 306/494 (61.9 %) met Eeles. *CHEK2*+ patients who met Chompret criteria (CHEK2+ LFS) included 12 1100delC mutation carriers and 18 non-1100delC mutations. No *CHEK2*+ LFS patients reported personal/family hx of ACC. No SAR was reported in non-1100delC carriers. Four patients had multiple LFS cancers: 2/18 (11 %) non-1100delC and 2/12 (16 %) 1100delC carriers. 6/12 (50 %) *CHEK2*+ LFS patients with 1100delC mutations reported BR diagnosed < 36 compared to 6/18 (33.3 %) non-1100delC carriers. 6/12 (50 %) *CHEK2*+ LFS patients with 1100delC mutations reported family hx of more than one LFS cancer compared to 7/18 (38 %) for non-1100delC carriers. This study confirms the presence of LFS/LFL phenotypes in a subset of *CHEK2*+ patients with both 1100delC and non-1100delC mutations.

Referrals to Genetic Counseling in Patients with Breast Cancer Based on National Comprehensive Cancer Network Guidelines

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Indications for referring to cancer genetic counseling and considering genetic testing for *BRCA1/2* are provided by the National Comprehensive Cancer Network (NCCN) Guidelines. This study is a retrospective review over a 5 year period of patients diagnosed with breast cancer who are found to have at least one of three characteristics that would qualify for genetic counseling and BRCA testing according to NCCN guidelines: 1) diagnosed <=45 years of age; and/or 2) triple negative breast cancer (TNBC) <=60 years of age; and/or 3) those who are male. Data was collected from the tumor registry at The Hospital of Central Connecticut and was compared to our genetic counseling patient database. From 2010 to 2014, there were 100 diagnoses <=45 years of age, 37 diagnoses of TNBC <=60 years of age and 2 males, for a total of 126 distinct patients meeting criteria for genetic counseling and genetic testing. Overall, 55 % of patients in this study were referred to genetic counseling. Of the eligible patients diagnosed in 2010, 2011, 2012, 2013, and 2014 the referral rates to genetic counseling were 30 %, 54 %, 44 %, 75 % and 61 %, respectively. Our findings in 2010 are comparable to other studies on women with early-onset breast cancer; however, a notable increase in referrals occurred over the 5 year time period. Of the 69 patients who were referred to genetic counseling, 96 % were seen. Of those 66 that were seen for genetic counseling, 97 % elected to proceed with genetic testing. One female with non-TNBC diagnosed <=45 years of age was found to carry a deleterious *BRCA2* mutation resulting in an incidence of 1.6 % in the cohort who had genetic testing (*n*=64). Based on these findings, our cancer committee has implemented a policy to add a notification to the pathology reports of all cases of triple negative breast cancer regarding the NCCN guideline recommendation to refer the patient to genetic counseling for consideration of genetic testing.

Determining the Clinical Significance of a *MSH2* Variants of Unknown Significance in a Family with Lynch Syndrome

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We report a family of Ashkenazi Jewish descent with a history consistent with Lynch syndrome. The proband initially presented in his early 40's with stage II adenocarcinoma in the transverse colon and underwent surgical resection without additional adjuvant treatment His oncology evaluation identified multiple paternal relatives with cancers consistent with Lynch syndrome. His tumor was found to be *microsatellite instability (*MSI*)* high with *immunohistochemistry* (IHC) loss of expression of MSH2 and MLH1. His younger sister was diagnosed during the same time period with tubulo-villous adenoma in the sigmoid colon. His paternal uncle was diagnosed with bladder and prostate cancer at age 63, with a history of colon polyps. The prostate carcinoma was notable for IHC loss of MSH2. The paternal grandmother was diagnosed in her 40's with uterine carcinoma, two metachronous occurrences of colon carcinoma in her 60's and ureteral carcinoma in her 60's as well. The proband's initial clinical sequencing of *MSH2* and *EPCAM* deletion results were inconclusive. As part of a research genetics study, six of the family members underwent combined exome and low fold coverage whole genome sequencing. This included the unaffected mother of the proband. Exome and whole genome sequencing analysis identified a MSH2 variant [c.1784 T>G, p.L595R] common to all the affected individuals compared to other germline coding variants. Per whole genome sequencing, no large genomic deletions were present in other causative genes of Lynch syndrome. In silico pathogenicity analysis (MAP-MMR) indicated a high likelihood of deleterious impact. Clinical diagnostic sequencing was repeated and the *MSH2* mutation was reclassified as causative. This case highlights the challenge of variant classification in the clinical setting and illustrates the diagnostic utility of variant of uncertain significance (VUS)-related segregation analysis in the era of clinical whole genome and exome sequencing, as well as genetic counselor involvement in variant reclassification.

Forget the Guidelines? Atypical Presentations of Well-Defined Hereditary Cancer Syndromes

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The landscape of cancer genetic testing has changed dramatically in recent years due to the cost-effectiveness of next-generation sequencing technologies and overturning of gene patenting. Clinical testing has largely shifted towards the use of multigene panels. It has been demonstrated that multigene panel testing identifies actionable gene mutations in probands with atypical presentations who may not meet classical testing criteria. The current case series reports three such patients. Proband 1 is a 69-year old male with 3 primary cancers: gastroesophageal junction adenocarcinoma, renal cell carcinoma and gastric adenocarcinoma. A 29-gene panel identified a pathogenic *BRCA1* deletion. This patient did not meet National Comprehensive Cancer Network (NCCN) testing criteria for *BRCA1/2*. Proband 2 is 67-year old female with bilateral breast cancers. The patient met NCCN criteria for *BRCA1/2* testing only. A 9-gene panel revealed a pathogenic *PMS2* mutation. Proband 3 is a 44-year old female with a history of breast cancer diagnosed at age 43, with a negative family history. A 25-gene hereditary cancer panel revealed a pathogenic *PMS2* deletion. The patient met NCCN criteria for *BRCA1/2* testing only. These cases add to the growing body of evidence that high-risk cancer predisposition genes may have a wider phenotypic spectrum than previously appreciated. This raises two questions for genetic counseling practice. First, should actionable cancer predisposition genes with established management guidelines be considered a single entity for diagnostic genetic testing? Reanalysis of testing criteria may be necessary to provide appropriate patient care and risk-reduction in patients with hereditary cancer syndromes. Second, what screening and management guidelines should be used for patients with atypical presentation? Guidelines for hereditary cancer syndromes have been developed based on risk figures gleaned from high penetrance families. These recommendations

may need to evolve as we learn more regarding the phenotypic spectrum of these conditions.

Pedigree Modeling Demonstrates that Family History Performs Poorly for the Identification of Women with Inherited Risks for Breast Cancer

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Hypothesis/Purpose: Women with an estimated >20 % lifetime risk of breast cancer are candidates for more aggressive clinical management including screening at younger ages, at more frequent intervals, and with more sensitive technologies. We utilized pedigree simulation to test the hypothesis that the majority of patients carrying pathogenic variants (PVs) of moderate to high penetrance in breast cancer-associated genes cannot be identified by family history analysis. Methods: We utilized computerized pedigree simulation and statistical modeling to estimate the probability that a female proband carrying a PV conveying a moderate or high increase in breast cancer risk, will be identified as having at least a 20 % lifetime breast cancer risk using the Claus model. Moderate penetrance and high penetrance were defined as a 24 % or 50 % female breast cancer risk to age 79, respectively. Simulated pedigrees were one-sided and limited to either the maternal or paternal side segregating the disease allele. Pedigrees were moderate in size, spanning 3 generations with sibships comprised of 2 or 5 individuals. Results: Simulated analysis of moderately and highly penetrant pathogenic breast cancer variants failed to identify >75 % and >91 % of appropriate patients by family history analysis, respectively, in sibships composed of 5 individuals. When considering sibships composed of 2 individuals, this result increased to >88 % and >95 % for moderate and high penetrance models. Conclusions: Pedigree simulation demonstrates that family history analysis alone fails to identify the majority of patients carrying PVs in breast cancer risk genes. Therefore, genetic testing is critical for identifying women who are candidates for modified medical management under current professional society guidelines. Although questions remain about the feasibility of population screening this study demonstrates a potential benefit of broad pan-cancer testing over family history based cancer-specific testing for patients who have been targeted for evaluation of inherited cancer risk.

Utilizing Kentucky Cancer Registry Data to Evaluate Cases Appropriate for Referral to Genetic Services for Hereditary Breast and Ovarian Cancer Syndrome and Lynch Syndrome, 2009–2012

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Background: It is estimated that over 1 million people in the U.S. have Hereditary Breast and Ovarian Cancer syndrome (HBOC) or Lynch syndrome (LS). However, most of these individuals remain undiagnosed. This study utilizes Kentucky Cancer Registry (KCR) data to estimate the number of cases of breast, ovarian, fallopian tube, colorectal and endometrial cancers diagnosed between 2009 and 2012 that would meet select guidelines for referral to genetic services. Methods: Breast, ovarian, fallopian tube, colorectal and endometrial cancers diagnosed between 2009 and 2012 were obtained from KCR. Evidence-based guidelines from National Comprehensive Cancer Network, Evaluation of Genomic Applications in Practice and Prevention, and the American College of Medical Genetics and Genomics and NSGC were used to determine the number of cases that met specific criteria for referral to genetic services. Descriptive statistics were performed and referral groups were compared using chi-square statistics. Geo-spatial distribution of the cases across counties and Area Development Districts in Kentucky was subsequently determined for 2012. Results: Of the 28,109 cancer cases diagnosed in Kentucky between 2009 and 2012, 15,270 (54.3 %) were determined to meet guidelines for referral including 4,022 cases of breast cancer, 1,057 cases of ovarian and fallopian tube cancers, 9,815 colorectal cancers and 376 endometrial cancers. Review of cases by county for 2012 showed that cancer cases appropriate for referral occur in every county, but only 10 % (12/120) of Kentucky counties and 60 % (9/15) of ADDs were equipped with genetic counseling services. Discussion: This study represents the first analysis of Kentucky Cancer Registry data to identify cancer cases appropriate for referral to genetic services. Identification of patients with HBOC and LS allow planning for cancer prevention, screening, and treatment in index cases and their relatives. Population-based programs for the identification of patients that would benefit from genetic services should be considered in Kentucky. In order to accommodate additional genetic counseling referrals from such programs, efforts should be made to expand the genetic counseling workforce in Kentucky.

Clinical Impact of Multi-Gene Testing for Hereditary Breast and Ovarian Cancer in a Large Representative Population

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3. Invitae

The practice of genetic testing is rapidly evolving with the recent introduction of multi-gene panels, however the clinical impact of these tests is not yet fully understood. For patients without *BRCA1/2* mutations management is traditionally guided by personal and family history, although additional (non-*BRCA1/2*) genes can contribute additional information. We sought to understand how often this information would change patient management recommendations in a large representative clinical cohort. We used similar 25 or 29 gene panels to test more than 1,000 patients, all of whom were enrolled prospectively at three academic medical centers and all met National Comprehensive Cancer Network guidelines for hereditary breast and ovarian cancer evaluation. We established a uniform algorithm based on current practice guidelines to recommend management actions for the non-*BRCA1/2*-positive individuals, and we evaluated which of these recommendations would represent changes in management over and above any recommendations based on personal and family history alone. In total, 63 patients were identified with pathogenic or likely pathogenic mutations in non-BRCA1/2 genes, consistent with published prevalence studies in similar cohorts. We found that the majority of these findings (55 %) would result in consideration of additional screening and/or prevention measures for the patient. Moreover, we found that genetic testing of first-degree family members would also be warranted given that 70 % of mutation positive relatives would also have a recommended management change. We conclude that in appropriately-referred patients, multi-gene panel testing yields clinically relevant findings with potential management impact for substantially more patients than does BRCA testing alone. Thus, this approach may improve care for many mutation-affected individuals in the short term, and in the long term should lead to the development of additional evidence-based guidelines for at-risk individuals.

Testing Relatives of Moderate Penetrance Breast and Ovarian Cancer Gene Mutation Carriers: Current Practices of Genetic Counselors

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Although moderate penetrance cancer genes are commonly used in the evaluation of hereditary breast and ovarian cancer susceptibility, their relevance to the cascade testing and medical management of at-risk relatives is less certain at present. We report current practices of genetic counselors regarding testing relatives of moderate penetrance breast and ovarian cancer gene mutation carriers. As part of an online survey conducted through NSGC, participants were asked about their counseling of family members through a series of closed- and open-ended questions. Eligible participants consisted of healthcare providers who had provided genetic counseling to at least one patient who tested positive for a pathogenic or likely pathogenic germline mutation in one of the following genes through a hereditary cancer panel: *ATM, BARD1, BRIP1, CHEK2, FANCC, MRE11A, NBN, PALB2, RAD50, RAD51*, *RAD51C, RAD51D*, and *XRCC2*. A total of 124 respondents were included in the final analysis. For most genes (10/13), the majority of respondents offered testing for the known familial mutation to relatives. If a family member tested negative, most respondents explained that it was unknown whether that individual's cancer risk was elevated above that in the general population and continued to offer high-risk cancer screening. Major themes identified in free-text responses included: (1) making the decision of whether testing would be relevant for a particular family member on a case-specific basis, (2) emphasizing the importance of pre-test counseling for family members, and (3) exercising caution regarding management recommendations for family members who tested negative for the known familial mutation. These data provide insight into how moderate penetrance cancer gene mutations are being incorporated into family-level testing and medical management despite uncertain cancer risks.

Familial Cancer Syndromes in African American Women with Ovarian Cancer

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Ovarian cancer (OVCA) has the highest mortality rate of all gynecologic cancers in the United States, particularly among African American women. Familial syndromes are associated with 10–15 % of OVCA; however, these syndromes have not been well-characterized in African American families. We describe cancers seen in Hereditary Breast and Ovarian Cancer (HBOC), Lynch Syndrome (LS), Cowden Syndrome (CS), and germline p16 mutations (p16) in African American women with and without OVCA. African American women with OVCA (ovarian, peritoneal and fallopian tube cancers) and healthy age-matched controls were identified from 10 sites between 2010 and 2014. These sites comprise the African American Cancer Epidemiology Study, and include 469 cases and 705 controls. A structured telephone questionnaire was administered to collect information on demographics, reproductive history, medical conditions, and family history of cancer (parents, full and half-siblings, children). Unconditional logistic regression models were created to estimate odds ratios and 95 % confidence intervals. Individuals with OVCA were about 40 % more likely to have a family history of HBOC-related cancers in a first degree relative than those without OVCA, after adjusting for study site, age, body mass index, education, age at menarche, number of live births, and number of first degree relatives (OR=1.41, 95 % CI: 1.04, 1.91). Cases were also more likely to have a family history of LS-related cancers (OR=1.32, 95 % CI: 1.00, 1.73), CS-related cancers (OR=1.51, 95 % CI: 1.11, 2.04) and p16-mutation-related cancers (OR=1.56, 95 % CI: 1.18, 2.07) after adjustment. For all syndromes, the association was strengthened as the number of affected relatives increased (p-trend: 0.01, 0.08, 0.04, and 0.003, respectively). This study documents for the first time that African American women with OVCA are more likely to have first degree relatives with cancers associated with known cancer syndromes, and their unaffected relatives may benefit from enhanced surveillance.

Pathogenic Mutations Identified in Patients with 6 or More Colon Polyps

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Hypothesis/Purpose: Testing patients at risk for hereditary colorectal cancer has traditionally posed a challenge for clinicians. Personal and family histories do not always meet the testing guidelines, even when the history appears suggestive to a clinician. At other times, criteria may be met for multiple syndromes. This analysis reviewed results from a hereditary cancer panel test to explore the how well polyp count might have predicted genetic diagnosis. Methods: Pathogenic mutations, as identified by a 25 gene hereditary cancer panel, were noted for all patients for whom a minimum of six polyps had been documented on the laboratory test request form. The polyp count, personal and family cancer history were reviewed for each patient. The panel included *BRAC1, BRAC2, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDKN2A* (p16INK4A and p14ARF), *CDK4, TP53, PTEN, STK11, CDH1, BMPR1A, SMAD4, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD51C* and *RAD51D*. Results: In total, 1017 patients were identified as having six or more polyps and, of these, 145 patients (14 %) were found to carry pathogenic mutations. The majority of the mutations were identified in the APC gene (54 patients) and biallelic *MUTYH* (15 patients). However, of these 69 patients, 24 (35 %) had less than 20 polyps. Eight of 25 patients (32 %) identified with a mutation in a Lynch syndrome gene had greater than 20 polyps. Of these patients with Lynch syndrome, all met Revised Bethesda

criteria and half met Amsterdam II. Eleven patients had mutations in other polyposis genes and 40 had mutations in genes unrelated to colon cancer with *BRCA2* (13 patients) being most common in this group. Conclusions: Although a thorough personal and family history are very important when selecting hereditary cancer testing among patients at risk for colon cancer syndromes, this sample of patients with polyposis illustrates an advantage of a multigene panel since polyp count may not indicate the single most appropriate hereditary colon cancer test.

Outcomes of Cancer Patient-Oncologist Interactions Concerning Familial Risk of Cancer and Referral to Cancer Genetics Services

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Background: Little is known regarding patient-oncologist communication about cancer genetics. We aimed to better understand cancer patients' interest in discussing familial cancer risk with an oncologist and communications on this topic. Methods: The parent study, "Improving Patient Doctor Communication (IPDC)," included 137 African Americans aged 25–85 with newly diagnosed breast, colorectal, or lung cancer. Data from participants randomized to receive an intervention with a question prompt list (QPL) and a visit with a communication coach prior to seeing a medical oncologist to discuss treatment (n=36) were analyzed in this study. Audio recordings of coaching sessions were reviewed to assess patients' interest in discussing familial risk with their oncologist. Video recordings of the patient-oncologist encounter were reviewed for patients indicating interest in discussing familial risk and for whom a video was available (n=14). Videos were coded to identify and describe conversations about familial risk, family history, features of hereditary cancer, cancer screening, tumor testing, previous genetic counseling, and referral to genetics. Results: Most patients (n=22, 61.1 %) indicated interest in discussing familial risk; reasons included concerns about relatives' risks or wanting to increase awareness in the family. Lack of interest was due to having already discussed familial risk with another provider or previous referral to genetics. Familial risk was discussed in just over half of oncology visits (n=8/14, 57 %); most discussions (n=5, 63 %) were initiated by the patient. Oncologists asked about family history in half of the visits. Six patients were appropriate for genetics referral; of these, 4 were referred. Conclusions: Most patients in this study were interested in discussing familial cancer risks with their oncologist. However, during the oncology appointment, only about half of those interested actually discussed the topic. Most oncologists discussed familial risks when the subject was raised and often made appropriate referrals for genetic counseling.

Impacts of Targeted Population Screening Program Implementation on a Cancer Genetics Clinic

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There has been a recent call for broader hereditary cancer screening. Our cancer genetics program implemented a screening process to identify individuals at increased risk for hereditary cancer. We hypothesized that implementing the screening program would significantly increase numbers of patients seen, genetic tests ordered, and mutations detected. A family history-based screening tool developed by the Centers for Disease Control and Prevention (CDC) was modified and used to identify high-risk patients receiving mammograms starting in October 2011. Our cancer genetics department staffs both private (insured) and public (underserved) clinics. From 2011 to 2014, >35,000 insured and >62, 000 underserved patients were screened, with those identified as high-risk being navigated to the cancer genetics clinic. Numbers of patients seen, tests ordered, and mutations detected were tracked across all sites from 2007 to 2014 to compare pre- and post-screening. The number of patients seen almost doubled after implementing population screening (1, 401 in 2011 vs. 2,679 in 2014), and the proportion of patients tested increased (68 % vs. 80 %, on average). The absolute number of mutations identified increased, but proportion of positive tests decreased, with a pre-screening average rate of 16 % versus a post-screening average rate of 12 %. These effects are observed more clearly in the underserved population, in which a large proportion of patients seen were identified through the screening program. In this group, total patients seen increased over 3-fold (279 vs. 893). On average, the proportion of patients tested increased after program implementation (68 % vs. 78 %), and mutation identification rate decreased (18 % vs. 9 %). Our population screening program substantially increased clinic and testing volumes but decreased the mutation positive rate. Implementing such screening will increase the number of at-risk patients receiving genetic counseling services but also likely require the addition of both genetic counselors and ancillary staff to take on the significant increase in volume.

An Investigation of Women at High Risk for Hereditary Cancer Who do not Utilize Genetics Services: What are They Communicating to Their Families?

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Research exploring genetic risk communication in families often focuses on families that have already had genetic counseling and/or testing. For this study, women who were informed that they are at high risk for hereditary cancer based on family history but did not utilize genetics services were interviewed regarding their communication of hereditary cancer risk to other family members. Telephone interviews (n=12) were conducted using a semi-structured guide with open-ended questions. Inductive and cross-case methods were used for data collection and analysis to identify themes. Communication of cancer risk primarily involved first-degree family members and often involved other women in the family. Females played an important role in information dissemination. The interviewees' knowledge of hereditary cancer was limited; therefore risk communication focused mostly on lifestyle and environmental factors rather than inherited risk. Communication was more frequent around the time of diagnosis or was triggered by diagnosis of other friends/family members. Intentions for communicating risk included increasing family cohesiveness, increasing family members' awareness of cancer risk, and advocating for health of the family. Barriers to uptake included interviewee having an inaccurate perception of hereditary cancer risk, having a good outcome after diagnosis (thus less concerned about cancer recurrence or diagnosis in other relatives), and feeling less urgency for being tested due to interviewees' lack of biological children who could inherit a cancer susceptibility mutation from them (n=3). When asked about genetic counseling, interviewees were interested and thought such services might be useful, but lacked the knowledge to appreciate value or personal relevance. These findings suggest the importance of continued education related to hereditary versus sporadic cancer, and increasing general awareness about genetic counseling. Since communication is frequent around the time of cancer diagnosis, this may be the optimal time to refer patients to a genetic counselor.

Pontocerebellar Hypoplasia Type 6: A Diagnostic Odyssey and Genetic Counseling Dilemma

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Pontocerebellar hypoplasia represents a group of autosomal recessive disorders characterized by progressive neurological degeneration, infantile encephalopathy and defects in the mitochondrial respiratory transport chain. Pontocerebellar hypoplasia type 6, (OMIM # 611523), is caused by mutations in the nuclear encoded RARS2 gene. We present a patient with mitochondrial dysfunction, secondary to pontocerebellar hypoplasia type 6. In reaching this diagnosis, familial cancer predisposition was an incidental finding. The patient presented with encephalopathy, hypoglycemia and lactic acidosis. Muscle biopsy showed mitochondrial complex IV deficiency. The patient passed away due to respiratory failure at the age of 18 months. Genetic testing included a comprehensive mitochondrial disease panel, which revealed two mutations in *RARS2*, in addition to a paternally inherited pathogenic mutation in the FH gene. In the homozygous form mutations in FH cause fumerase deficiency (OMIM #606812); in the heterozygous form hereditary leiomyomatosis and renal cell cancer (OMIM#150800). The disclosure of these incidental results demonstrated the importance of pre-test counseling, the principle of autonomy and recognizing differing coping styles and defense mechanisms amongst family members. In testing a sick child, parents may not expect to find out information that may have a direct impact on their own health and the health of relatives. It may also be difficult to balance the desire to learn the cause of a child's illness against the possibility of learning health information one may not wish to know about oneself. In this case, the autonomy of the family was impacted as they may not have wanted to be aware of their increased risk for cancer. Coping styles and defense mechanisms illustrated by this family included "plan", "denial" and "self-controlling". Overall, this incidental finding created additional stress and anxiety in the family, in the midst of an already stressful situation.

One Clinic's Experience with *CHEK2* Mutations Other than c.1100delC

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Cell cycle checkpoint kinase 2 (CHEK2) is a checkpoint kinase important for DNA damage signaling and repair. Current data estimates heterozygous mutations in *CHEK2* increase risk for breast and colon cancer and possibly prostate, thyroid and kidney cancer. Here we describe the outcomes from approximately 15 months of germline testing for *CHEK2* in families with breast, colon and other cancers at the Stanford Cancer Genetics Clinic. Data was collected from January 2014-March 2015. 786 individuals with personal or family history of breast and other cancers were offered a panel that included *CHEK2*. 22 individuals (3 %) were found to carry a heterozygous germline *CHEK2* mutation. 17 (77 %) of these were mutations other than c.1100delC. The only recurring non-c.1100delC mutation was p.Ile157Thr. Six individuals in our cohort were found to carry this variant (27 %). All of these individuals had a personal or family history of breast cancer; two had a personal or family history of colon cancer. Our six unrelated families also reported a history of pancreatic, uterine, ovarian, thyroid, melanoma and prostate cancer, although for most cases the origin of the mutation is unknown. There is discordance in the classification of this variant by testing laboratories. Functional studies have demonstrated that this alteration interferes with DNA damage response and epidemiological data support pathogenicity, however this variant is found in NHLBI control populations and some data support lower cancer risk, suggesting this is a lower penetrance mutation. Our recommendations for patients with *CHEK2* mutations include high risk breast cancer screening with mammogram and MRI for women, colonoscopy every 3–5 years and additional screening tailored to an individual's personal and family history. Continuing data collection with panel testing and identification of non-c.1100delC *CHEK2* mutations will contribute to understanding of the *CHEK2* phenotype and will help clarify guidelines for cancer screening.

Coordinating Laboratory and Clinical Data to Incorporate Endometrial Tumor Testing into the Universal Lynch Syndrome Screening Program at Geisinger Health System

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Background: Universal Lynch Syndrome screening (ULS) is defined as tumor screening of all individuals newly diagnosed with colorectal (CRC) or endometrial cancer (EC). ULS screening has been implemented in multiple health systems and is part of the Healthy People 2020 initiative. ULS was instituted at Geisinger Health System (GHS) in 2012 for CRC. Current ULS for CRC includes immunohistochemistry (IHC) screening of all CRC resected tumors regardless of age, with reflexive *BRAF* and promoter hypermethylation (PHM) testing as appropriate through pathologists. EC tumor screening was limited to age <=60 or age >60 with specific tumor histology. No protocols were in place for reflexive PHM testing in EC tumors. Methods: Two genetic counselors and a molecular pathologist evaluated all EC patients with IHC testing since 2012 to identify care gaps and presented results to pathologists, genetics services, gynecologic oncologists and ethics to facilitate inclusion of EC in the ULS program. Results: Since 2012, 161 EC patients were screened by IHC (N=152 <=60 and N=19 >60); of whom 30 (18 %) had loss of MLH1/PMS2 and 11 (7 %) had MSH2 or MSH6 loss. Only 10 patients with MLH1 loss (33 %) had PHM testing to differentiate between germline vs. somatic etiology. Of the 20 remaining EC patients, 6 (30 %) were referred to genetics without determination of tumor etiology and 14 (70 %) had no additional follow-up. 91 % of patients (10 out of 11) with MSH2 or MSH6 loss were referred to genetics. Based on the benefits identified through the ULS program for CRC previously adopted, multiple stakeholders worked together to develop protocols and facilitate policy change to include EC screening in the ULS program. Conclusion: We determined that limited EC tumor screening potentially creates missed opportunities to identify LS patients. Engagement of multiple stakeholders was required to reach agreement that adding EC tumor screening to the existing ULS program with reflexive PHM testing by pathologists will result in improved identification of LS patients and facilitate appropriate care.

Phenotype Comparison Between Founder and Non-Founder *CHEK2* Mutation Carriers

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The phenotype of individuals and families with *CHEK2* mutations is currently not well defined, particularly for those harboring non-founder *CHEK2* mutations. The purpose of this study was to assess the phenotypes and molecular characteristics of *CHEK2* mutation carriers in a multi-gene cancer panel cohort with a focus on comparing phenotypes of founder and non-founder mutation carriers. Clinical histories of

patients with *CHEK2* pathogenic mutations or likely pathogenic variants reported on multi-gene panel testing from March 2012-December 2014 were reviewed, including personal and family history of breast (female and male), multiple primary breast, colorectal, ovarian, thyroid, prostate, kidney, and endometrial cancers. Clinical history information was obtained via clinician-report through test requisition forms. *CHEK2* mutations were detected in 594/23,555 individuals (2.5 %). Individuals with additional mutations in non-CHEK2 genes (n=52) or with biallelic *CHEK2* mutations (n=7) were excluded from analysis, as were those for whom no personal or family history information was provided by the clinician when appropriate (n=11). Family members known or inferred to be negative for the familial *CHEK2* mutation were also excluded from analysis. *CHEK2* mutations were further categorized as founder mutations (n=422) or non-founder mutations (n=113). Founder mutations were classified as c.1100delC (n=223), c.1283C>T (p.S428F) (n=46), c.444+1G>A (n=12), c.470T>C (p.I157T) (n=125), and CDS8_9del (EX9_10del) (n=16). Clinical histories of non-founder mutation carriers were compared against founder mutation carriers using Fisher's exact test. No significant differences were observed between clinical histories of *CHEK2* non-founder and founder mutation carriers. These data suggest that cancer risks reported in founder populations may be generalizable to all *CHEK2* mutation carriers.

Assessment of Constitutional Mismatch Repair Deficiency Syndrome Testing Criteria in a Pediatric Cancer Genetics Clinic

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Introduction: Constitutional mismatch repair deficiency syndrome (CMMRD) predisposes to pediatric-onset cancers and is caused by biallelic defects in mismatch repair (MMR) genes. CMMRD diagnostic criteria have been proposed to guide the testing of patients with cancer. Using these criteria, a score of 3 points is the minimum needed to consider CMMRD testing. As the clinical utility of this system is yet to be determined, a preliminary assessment was performed. Methods: Twelve cancer patients referred to the Cancer Predisposition Program at St. Jude Children's Research Hospital were assessed for CMMRD. All patients had a testing criteria score of >=3. After clinical assessment and genetic counseling, MMR gene testing was performed. Reason for referral, cancer diagnosis, demographics, MMR immunohistochemistry (IHC) results and family history information were collected. Descriptive statistics were used to evaluate the relationship between testing criteria score and the likelihood of having a CMMRD diagnosis. Results: The most common primary tumor types were brain (n=5; 41.6 %) and hematologic (4; 25 %). Eight (75 %) patients were referred for signs of NF1 (café au lait spots or neurofibroma). Only 1 family history met Lynch syndrome Amsterdam criteria. Testing revealed 4 patients (33.3 %) with a molecular diagnosis of CMMRD (testing criteria scores: 3, 6, 6, 8). One (8.3 %) patient (testing criteria score: 4) had a single MMR variant of unknown significance. The remaining cases had no MMR gene alterations (testing criteria scores: 3–5). Discussion: Although the current CMMRD testing criteria scoring system lacks specificity, these results suggest that they should be integrated into the evaluation of children with cancer, given that one third of patients in this small group were diagnosed with the condition. Larger cohorts with complete clinical and genetic evaluation will improve our ability to assess and optimize the testing criteria. Future blood-based functional assays to assess MMR deficiency may also assist in guiding testing.

Comparing Yields and Referral Criteria for the Lynch/Colorectal High Risk Panel and the Colorectal Cancer Panel

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Introduction: The growing availability of multi-gene panels for inherited cancer susceptibility can present clinicians with difficult decisions concerning the type of panel to order, especially for patients with atypical clinical presentations. In addition, some of the less well-described genes included on many panels may not have standard management guidelines and therefore present a challenge to translating results into clinical care. Purpose: The aim of this study was to compare the yield of pathogenic/likely pathogenic variant (PV/LPV) results from a seven-gene Lynch/Colorectal High Risk Panel (high-risk panel) with well-established phenotypes and management guidelines versus a Colorectal Cancer Panel (CRC panel) consisting of these genes and nine more that have recently been associated with increased colon cancer risk. Methods: We retrospectively reviewed our data for individuals who underwent testing with a seven gene high-risk panel or a 16-gene CRC panel, to identify those patients with a PV/LPV. We then assessed the clinical histories of those individuals carrying a PV/LPV in a gene in the CRC panel not included in the high-risk panel. Results: Of 679 high-risk panel tests, 93 had PV/LPV (13.7 %) results, while 107/885 (12.1 %) had PV/LPV results on the CRC panel. Of these 107 cases with a PV/LPV result on the CRC panel, 41 (38.3 %) had findings in genes not included in the high-risk panel; *CHEK2* (20), *ATM* (7), *PTEN* (6), *SMAD4* (4), *STK11* (2), *CDH1* (2), *BMPRIA* (2). Of the 41 cases with a PV/LPV in the aforementioned genes, 35 (85.4 %) met at least one well-established CRC testing guideline. Two individuals met Amsterdam criteria, 19 had a personal or family history that met Bethesda guidelines/endometrial cancer <50 and 18 had >10 colon polyps. Conclusions: Many of the PV/LPV identified on the CRC panel would have been missed if the high-risk panel had been ordered. Therefore, a broad panel might be considered, even in cases with a clinical history consistent with published testing guidelines for well-established genes, in order to capture unexpected findings.

Complex Counseling Issues Regarding Cancer Panels: Genetic counselors' Experiences Regarding Communication of Reproductive Risks Associated with Autosomal Recessive Conditions

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Objectives: The development of hereditary cancer genetic testing panels has altered genetic counseling practice. Mutations within certain genes on cancer panels pose not only a cancer risk, but also a reproductive risk for autosomal recessive conditions such as Fanconi anemia, constitutional mismatch repair deficiency syndrome, and ataxia telangiectasia. This study aimed to determine if genetic counselors discuss reproductive risks for autosomal recessive conditions associated with genes included on cancer panels, and if so, under what circumstances these risks are discussed. Methods: An online survey composed of 10 open and 14 closed ended questions was emailed through the NSGC listserv. The survey assessed cancer genetic counselors' experiences discussing reproductive risks with patients at risk to carry a mutation or variant of uncertain significance (VUS) in a gene associated with both an autosomal dominant cancer risk and an autosomal recessive syndrome (N=189). Results: Over half (n=82, 55 %) reported having discussed reproductive risks; the remainder (n=66, 45 %) had not done so. Overall, genetic counselors who reported discussing reproductive risks primarily did so when patients had a positive result and were of reproductive age. Reasons for not discussing these risks included when a patient had completed childbearing, or when a VUS was identified. Genetic counselors with more years of experience, and those spending a greater percentage of time in cancer genetic counseling, were more likely to discuss reproductive

risks ($p<0.05$). Most counselors discussed reproductive risks after obtaining results and not during the informed consent process. Conclusions: There is inconsistency in if and when the discussion of reproductive risks is taking place. The wide variation in these reproductive risk discussions suggests a need to develop professional guidelines for when and how discussions of reproductive risks for autosomal recessive conditions identified through cancer panels should occur with patients.

A Rare Presentation of Familial Adenomatous Polyposis

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Familial Adenomatous Polyposis (FAP) is a well-known multi-system hereditary cancer susceptibility syndrome which predisposes individuals to significant colonic polyposis; without intervention, colon cancer is virtually inevitable. Additionally, these individuals are at increased risk for several extraintestinal cancers, including papillary thyroid cancers, which, in rare occasions, may be the presenting manifestation of the disease. A significant proportion of individuals with a rare subtype of papillary thyroid cancer, cribriform-morular (CMPTC), have an underlying diagnosis of FAP. Due to its rarity and heterogeneity, the CMPTC may be either missed or misinterpreted as a more aggressive tumor. Our proband, a 19-year-old female was referred to our Institute for additional evaluation of a suspicious thyroid nodule. Previous thyroid biopsies noted atypical cells of indeterminate significance; re-review raised concern of a medullary thyroid cancer. Additional biopsies performed were consistent with a papillary thyroid cancer. Subsequent total thyroidectomy ultimately confirmed a multifocal papillary carcinoma, cribriform-morular type. Based on this pathology, the patient was referred for colonoscopy and clinical genetics consultation. Colonoscopy identified innumerable colon polyps; representative biopsies were consistent with an adenomatous pathology. Genetic testing of the APC and MUTYH genes ultimately confirmed the patient to have a deleterious APC gene mutation. Although the reported family history was negative for individuals known to have colon polyps and/or cancer, this mutation was confirmed to be maternally inherited. Based on this, her first-degree relatives had genetic counseling and subsequent testing, which confirmed a diagnosis of FAP in three more of these relatives. This case raises genetic counselor awareness of unusual presentations of FAP, demonstrates the importance of correctly identifying this rare thyroid cancer and supports the recommendation that individuals with CMPTC be referred for genetic counseling and assessed for FAP.

Recontacting Patients in the Age of Panel Testing: Cancer Genetic Counselors' Practice and Perspective

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The duty to recontact patients is an acutely pertinent topic in cancer genetics given the recent availability of hereditary cancer panels that allow for rapid analysis of multiple genes associated with cancer development. The development of practice recommendations on recontact in cancer genetics requires understanding the practice and perspective of cancer genetic counselors. From December 10, 2014-January 7, 2015 we conducted an online anonymous survey of cancer genetic counselors in the United States and Canada. Questionnaire domains included scope of recontact practice, factors influencing recontact practice, method of recontact, attitudes about recontact, and demographic characteristics. A total of 127 counselors responded to the survey, with 52 % (66) of respondents reporting that they have recontacted patients to offer updated diagnostic testing. Of those who reported recontact and continued the survey, 75 % reported recontact to offer hereditary cancer panel testing and 80 % to offer *BRCA1* and *BRCA2* rearrangement testing. Factors influencing recontact include "available resources/staff for recontact" (80 %), "available systems for recontact" (75 %), and "potential implications for the patient's family" (65 %). Respondents indicated that recontact for updated diagnostic testing is a shared responsibility between the provider and patient (43 %), or, mostly patient responsibility (49 %). A minority indicated that recontacting patients about updated diagnostic testing should be the standard of care for genetics providers (4 %). Outside of patient recontact, education of other providers was the most reported alternative method (57 %) to increase patient awareness of updated diagnostic testing. This empirical data offer insight into possible practice recommendations on recontact for updated diagnostic testing in cancer genetics.

Lifestyle Risk Factors Among Cancer Genetic Testing Patients

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Lifestyle influences cancer risk. Genetic counselors help clients understand and manage their risks. Traditionally genetic counseling has focused on medical interventions like screening, risk-reducing surgery, and medication. Lifestyle changes may be cheaper, more accessible, and helpful for multiple diseases. This study assessed cancer risk-relevant lifestyle factors for people who have had cancer genetic testing. Data came from the Health Information National Trends Survey (HINTS 4), with nationally representative phone and mail data, collected through 2013. The presented analyses selected variables relevant for American Cancer Society nutrition and physical activity guidelines. Lifestyle factors were assessed for people who had undergone testing for BRCA1, BRCA2, or Lynch Syndrome genes. Analyses used SAS v.9.3 SURVEY procedures. In exploratory analyses, lifestyle was compared with people who had not had genetic testing, adjusted for potentially associated ($p<0.10$) demographic factors. Among 3,016 HINTS respondents, 135 had cancer genetic testing. Average body mass index (BMI) for people who had testing was 27.8 (SE=0.62) kg/m2. 57.6 % were overweight or obese. 17.6 % did no physical activity of at least moderate intensity. On average, they reported sedentary behavior (e.g., watching TV) 3.4 (SE=0.472) hours daily. 62.6 % drank non-diet soda, and 22.6 % of these people drank soda every day. They most commonly ate 1–2 cups fruit (33.5 %) and 1–2 cups vegetables (34.8 %) daily. 23.8 % were current smokers. There were no differences in age, race, or education between those who did and did not have testing. People who had testing were more likely to be female and have higher income. Controlling for gender and income, having genetic testing was not a predictor of lifestyle. In conclusion, most people who have genetic testing for cancer susceptibility have at least one modifiable risk factor. Genetic counselors have opportunities to impact a client's cancer risk not only through risk-tailored medical procedures, but also through lifestyle modification recommendations.

Managing Uncertainty: Lessons Learned from Utilizing a Biallelic *MSH6* Variant of Uncertain Significance to Alter Clinical Care

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Introduction: Variants of uncertain significance (VUS) continue to be a significant challenge for providers and patients alike; no consensus exists

regarding what to do with these results. The value of communication between the laboratory and provider cannot be underestimated; it is indeed a two-way conversation with each source of information facilitating interpretation of the other. Here, we report a case where an *MSH6* VUS was used to guide clinical management, ultimately leading to the detection of asymptomatic tumors in the patient and eventual variant reclassification. Care Report: Our patient is of Palestinian ancestry and presented at age 12 with anaplastic astrocytoma. Constitutional Mismatch Repair Deficiency syndrome (CMMRD) was suspected due to the high grade nature of the brain tumor, presence of café-au-lait spots, and parental consanguinity. Results from a MMR gene panel test revealed a homozygous *MSH6* VUS: c.3701_3706dupAACTTG. Although the impact of this variant was unclear, based on the high level of clinical suspicion, CMMRD-related tumor surveillance was added to the patient's care plan. Upon colonoscopy, numerous polyps were identified, including 1 that was determined to be a mucinous adenocarcinoma. As a result, the patient underwent a total colectomy. The patient's sister, age 9 and with multiple café-au-lait spots, also tested positive for the homozygous *MSH6* VUS. She was subsequently noted to have extensive colonic polyps as well as lesions consistent with a diagnosis of gliomatosis cerebri. Discussion: In specific family and/or medical contexts, a VUS may have clinical utility. With our patient, we were able to detect and remove colon cancer before it metastasized and/or became inoperable. For our patient's sister, testing for the familial VUS enabled us to justify CMMRD-related tumor surveillance which detected many asymptomatic lesions. Sharing the aforementioned clinical information with the testing laboratory facilitated the ultimate reclassification of this variant as likely pathogenic.

Congenital Wilms Tumor in a Father and Daughter Found to Carry a Novel Truncating Mutation in the WT1 Gene

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Inherited mutations in the WT1 gene are associated with predisposition to syndromic and isolated Wilms tumor, genitourinary abnormalities, and nephrotic syndrome. Here, we describe a family with a novel *WT1* mutation located 5' to any other *WT1* mutations previously reported in the literature. The father of the proband had a history of bilateral Wilms tumor diagnosed in his first couple days of life in addition to unilateral cryptorchidism. He had a left nephrectomy at 3 days of age followed by preoperative chemotherapy with vincristine and dactinomycin, and a partial right nephrectomy at 7 months. In adolescence he went into renal failure and underwent renal transplant. Shortly after discovering his wife was pregnant with his first child, he was evaluated in a general genetics clinic and found to have a novel c.144C>G truncating mutation in *WT1*. The couple declined prenatal genetic testing, but underwent serial prenatal ultrasound surveillance that was unremarkable. On day of life one, abdominal ultrasound revealed a right renal mass. Postnatal genetic testing confirmed that the proband, a daughter, had inherited the familial *WT1* mutation. She was treated with vincristine alone and later with added dactinomycin. She underwent a partial right nephrectomy at 3 months of age, which confirmed the diagnosis of Wilms tumor. Both paternal grandparents tested negative for the familial *WT1* mutation; intriguingly, the paternal grandfather was affected with glomerulonephritis of unknown etiology at age 35. It remains uncertain whether the father's nephrotic syndrome was due to the *WT1* mutation, unrelated factors that also contributed to the grandfather's history of glomerulonephritis, or other factors, such as exposure to chemotherapy. This report of congenital Wilms tumor in a father and daughter supports the idea that early truncating *WT1* mutations can be highly penetrant and may be associated with a very early age of Wilms tumor development, as well as nephrotic syndrome and genitourinary abnormalities.

Hereditary Cancer Testing for Patients of Ashkenazi Jewish Ancestry in the Era of Panel Testing

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1. Myriad Genetic Laboratories, Inc.

Hypothesis/Purpose: Due to the high prevalence of 3 founder mutations in *BRCA1/2* among patients of Ashkenazi Jewish (AJ) ancestry, current National Comprehnsive Cancer Network guidelines recommend founder mutation testing for all AJ women with a personal history, or close relative diagnosed with breast or ovarian cancer at any age. A subset of AJ individuals with additional history are candidates for full analysis of *BRCA1/2* and current data suggests that this results in approximately a 10 % increase in mutations detected. However, with the advent of panel testing for multiple additional genes, we hypothesized that "reflexing" AJ patients to a panel following negative founder mutation testing would significantly increase the number of pathogenic variants (PVs) identified relative to *BRCA1/2* testing alone. Methods: We analyzed results from clinical testing of AJ patients with negative results for the 3 *BRCA1/2* founder mutations, who were then tested with a 25-gene hereditary cancer panel including *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, APC, MUTYH, CDKN2A, CDK4, TP53, PTEN, STK11, CDH1, BMPR1A, SMAD4, PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD51C*, and *RAD51D*. All patient information was obtained by health care provider report on the test requisition forms. Results: 2,667 patients of AJ ancestry underwent genetic testing. Of those, 4.8 % (129) tested positive for one of the 3 founder mutations. 2,217 patients went on to testing with the 25-gene panel and 2.4 % (54) were identified as having at least one pathogenic mutation, 22.2 % (12) of which were non-founder mutations in *BRCA1/2* mutations, and 77.8 % (42) in 14 other genes. This included mutations in *CHEK2* (16.7 %), *ATM* (11.1 %), and *MSH6* (7.4 %). Conclusions: An AJ patient in this cohort is 3 times more likely to carry a pathogenic mutation in a different inherited cancer gene compared with a non-founder mutation in *BRCA1/2*. This supports the hypothesis that the yield from multi-gene panel testing is significantly higher compared with comprehensive analysis of *BRCA1/2* alone for patients of AJ ancestry.

Outcomes of Multi-Gene Testing for Inherited Cancer Risk in Patients of Varied Ancestries

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Hypothesis/Purpose: Genetic testing outcomes can vary by patient ancestry, due to founder mutations, knowledge about variants, other biological/environmental risk factors, and disparities in access to services. We investigated the impact of patient ancestry on utilization and results from clinical testing with multi-gene panels that have recently emerged as an alternative to single gene/syndrome testing for assessment of inherited cancer risk. Methods: Results are from 74,095 female patients tested clinically with a 25 gene hereditary cancer panel. Clinical information was obtained from test request forms completed by ordering healthcare providers. Pathogenic variants (PVs) are those classified as deleterious or suspected deleterious. Results: Almost 50 % of the female sample reported White/Caucasian ancestry. Excluding patients with no specified ancestry (19.8 %), or multiple reported ancestries (11.3 %), the next three largest groups were Latin American/Caribbean (7.2 %), African (6.0 %) and Asian (2.6 %). The positive rate in the four most common ancestries for one or more PVs was 7.6 %, 7.4 %, 6.6 % and 7.6 %. Although there were differences in the prevalence of PVs in different genes by ancestry, the highest number of PVs in all groups was in *BRCA1* and *BRCA2*,

followed by the moderate penetrance breast cancer genes, *ATM*, *CHEK2* and *PALB2. CHEK2* mutations were notably more common in patients reporting White/Caucasian ancestry, due largely to the 1100del European founder PV. Evidence is emerging for the presence of additional founder mutations in other panel genes. Conclusions: There is evidence for underutilization of the hereditary cancer panel for non-White/Caucasian women based on the ancestry distribution in the U.S. population. Among the women tested, the positive rate for detection of one or more PVs was not strikingly different in any ancestry, and although there were differences in the distribution by gene, there is no evidence to suggest that the panel approach has benefits that are ancestry-specific.

Urologists' Current Practices in Screening and Treating Men with a Family History of Prostate Cancer

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Background: Family history is one of the few well-defined risk factors for prostate cancer (PC). Guidelines for PC screening are variable for high-risk men, and guidelines for treatment do not change in the setting of familial PC. There is limited data whether family history of PC is used in clinical urological practice. Therefore we surveyed urologists to assess whether current practice takes family history into account and affects their PC screening and treatment recommendations. Methods: Surveys were handed out to members of the Chicago Urological Society at the November 2014 meeting on prostate cancer. Survey questions explored urologists' frequency of family history collection and utilization of family history for screening and treatment recommendations for PC. Data were summarized and compared using descriptive statistics. Results: A total of 87 responses were included in the analysis, for a response rate of 60 % (87/145). The majority reported that they always collect family history when discussing risk (95 %) or screening (87 %), and recommended earlier screening for men with family history of PC in comparison to men with no family history. Although only 57 % reported always collecting family history when discussing treatment, it was evident more definitive treatment plans were adopted when presented with various family history scenarios. Eight percent of urologists would recommend prostatectomy for men diagnosed with low grade, low risk PC and no family history of PC versus 52 % who would recommend the same course of treatment when the patient had at least 1 first degree relative (FDR) who died of the disease. Conversely, 91 % of urologists would recommend active surveillance for men with low grade, low risk PC versus 47 % for those with at least 1 FDR who died of the disease. Conclusion: Despite the lack of literature to support familial PC patients needing more aggressive treatment, urologists were more likely to recommend definitive therapies, with their inherent side effects possibly contributing to the overtreatment problem in prostate cancer.

Identification of a Recurrent Pathogenic Variant in *BRIP1*

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Purpose: Pathogenic variants in *BRIP1* are known to be associated with an increased risk of breast and ovarian cancer; however, little is known about the spectrum of pathogenic variants seen in this gene.
Methods: We identified patients positive for pathogenic variants in *BRIP1* through clinical testing with a 25-gene hereditary cancer panel from September 20, 2013 to March 13, 2015. Patients were referred for panel testing due to a personal and/or family history of cancer. Results: 230 patients were found to have a pathogenic variant in *BRIP1*, 85 (37.0 %) had a personal diagnosis of breast cancer, 38 (16.5 %) had a personal diagnosis of ovarian cancer, and 100 were unaffected at the time of testing (43.5 %). Of the 230 patients identified to carry *BRIP1* pathogenic variants, 67 (29.1 %) were heterozygous for the variant c.2392C>T that truncates the protein at amino acid position 798. 31/67 (46.3 %) had a personal diagnosis of breast cancer, 6/67 (9.0 %) had a personal diagnosis of ovarian cancer, and 32/67 (47.8 %) were unaffected. The majority of patients positive for c.2392C>T reported to be of Western/Northern European ancestry (56.7 %), compared to 50.9 % in all patients with *BRIP1* pathogenic variants. Interestingly, the common Icelandic and Spanish variants (c.2040_2041insTT and c.1702_1703del) were not detected. Conclusions: A single truncating variant has been identified that constitutes 29.1 % of the total pathogenic variants in *BRIP1*. The types of cancer associated with c.2392C>T are similar to those seen with other *BRIP1* pathogenic variants. In this cohort, these findings highlight the importance of *BRIP1* as a breast and ovarian cancer predisposition gene.

Predispositions to Lymphoma: A Practical Guide for Genetic Counselors

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As with almost all cancers, the majority of lymphomas are sporadic yet rare hereditary predispositions exist. Identifying families with a predisposition to lymphoma has potential to decrease morbidity and mortality while also helping the individuals understand and adapt to the medical, psychological, and familial implications of disease. Cancer genetic counselors are aware that genomic instability syndromes, such as Li-Fraumeni syndrome, can predispose to lymphoma. In addition, recent technological advances have ushered in the identification of many new germline genetic syndromes predisposing to lymphoma, particularly in the area of immune dysregulation. Immune-mediated lymphoma predisposition has historically been sparsely discussed in the cancer genetic counseling literature but the integration of genetic counseling into immunology is bridging the two specialties. We aim to increase the awareness among genetic counselors and colleagues in oncology about familial lymphoma susceptibility and facilitate critical thinking in the face of a lymphoma risk assessment. We provide a synopsis of major concepts of lymphoma predisposition including genomic instability, role of oncogenic viruses, autoimmunity, proliferation/apoptosis imbalance, and chronic antigen stimulation. Syndromes typifying each of these mechanisms are discussed and a summary table with empiric risk estimates is provided. Clinical translation of this knowledge is aided by recommendations for targeted collection of personal and family history to guide risk assessment and testing. Lastly, genetic counseling issues including perceptions of the context, nature, and magnitude of lymphoma risk, as well as special issues in coping with lymphoma susceptibility are highlighted.

Cancer Incidence in First and Second Degree Relatives of BRCA Mutation Carriers

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Purpose: Mutations in the BRCA1 or BRCA2 genes are associated with increased risks for breast, ovarian, and several other cancers. The purpose of this study was to evaluate the incidence of cancers in first and second

degree relatives of BRCA mutation carriers compared to the general population. Methods: A total of 1,086 pedigrees of BRCA mutation carriers was obtained from a prospectively maintained, internal review board approved study of persons referred for clinical genetic counseling at The University of Texas MD Anderson Cancer Center. We identified 9,032 first and second degree relatives from 784 pedigrees which demonstrated a clear indication of parental origin of mutation. Standardized incidence ratios (SIRs) were used to compare the observed incidence of 20 primary cancer sites to the expected incidence of each cancer based on calculated risk estimates according to a subject's age, sex, and ethnicity. Results: BRCA1 families had increased SIRs for breast and ovarian cancer ($p<0.001$) and decreased SIRs for kidney, lung, Non-Hodgkin's lymphoma, prostate, and thyroid cancer ($p<0.001$). BRCA2 families had increased SIRs for breast, ovarian, and pancreatic cancer ($p<0.001$) and decreased SIRs for kidney, lung, Non-Hodgkin's lymphoma, thyroid, and uterine cancer ($p<0.0025$). Analysis of only first degree relatives ($n=4,099$) identified no decreased SIRs and agreed with the increased SIRs observed in the overall study population. It also identified an increased SIR for prostate cancer in BRCA2 families trending towards significance ($p=0.003$). Conclusion: We confirmed previous reports of an association between breast, ovarian, and pancreatic cancers with BRCA mutations as well as an association between prostate cancer with *BRCA2* mutations. Additional research to quantify the relative risks of these cancers for BRCA mutation carriers can help tailor recommendations for risk reduction.

Evaluating the Appropriateness of Hereditary Breast and Ovarian Cancer Genetic Referrals by National Comprehensive Cancer Network Guidelines and Predictive Risk Models

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Introduction: As awareness of Hereditary Breast and Ovarian Cancer (HBOC) syndrome continues to grow, so has the demand for genetic risk assessment and testing. These services can be utilized most effectively by ensuring that referrals for cancer genetic counseling are appropriate based on a personal or family history suggestive of HBOC. Purpose: We investigated whether referrals for cancer genetic counseling were appropriate by determining if patients met National Comprehensive Cancer Network (NCCN) Guidelines® Version 1.2014 for Breast and/or Ovarian Cancer Genetic Assessment and HBOC syndrome testing criteria, as well as their scores on the Breast Cancer Genetics Referral Screening Tool (B-RST) and BRCAPRO model. Methods: We conducted a retrospective chart review to collect information on patients seen within the Emory Department of Human Genetics (DOHG) and the Winship Cancer Institute High Risk Assessment Clinic (HRC) from 2008 to 2013. Full pedigrees and *BRCA1/2* test results were evaluated. Results: Of 367 patients analyzed, 94.8 % met NCCN risk assessment criteria and 92.4 % met testing criteria. In contrast, 42.2 % screened positive on B-RST while 13.1 % had a BRCAPRO score of >=10 % and 22.1 % had a score of >=5 %. Of the 214 patients who underwent BRCA testing, 14 (6.5 %) had a mutation. Among mutation carriers, 6 had a BRCAPRO score <5 % and 10 scored positive on B-RST. The specificities of BRCAPRO cutoffs of 5 % and 10 %, B-RST, and NCCN testing criteria were 79 %, 88 %, 52 %, and 4 %, respectively. Conclusions: While a large majority of patients referred met NCCN Guidelines®, most were not considered at high risk for HBOC by B-RST or the BRCAPRO cut offs of 5 % and 10 %. The guidelines did not appear to discriminate individuals at low risk to carry a BRCA mutation. Further studies evaluating the clinical usage of NCCN criteria and predictive risk models, along with more studies on HBOC penetrance in families with limited cancer histories, can help guide healthcare professionals in referring patients within this rapidly changing landscape of cancer genetic testing.

Yield of Genetic Testing for Hereditary Cancer Among Male Patients

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1. GeneDx

Background: Historically, genetic testing guidelines for hereditary breast and ovarian cancer (HBOC) focused on female probands with a clinical history. Despite recognition of prostate and pancreatic cancer as features of HBOC, published guidelines have only recently included these in testing criteria. Next generation sequencing has expanded cancer genetic testing, but testing of men remains limited. We sought to quantify testing in men and to determine the yield of pathogenic/likely pathogenic variants (PV/LPV) in men with breast, prostate or pancreatic cancer. Methfods: We reviewed the results of 1,635 men genetically evaluated for *BRCA1/2* and up to 27 additional high/moderate risk genes, including 184 with breast cancer, 116 with pancreatic cancer and 144 with prostate cancer. Results: In an unselected series of 25,755 inherited cancer genetic tests, 1,635 specimens were received from men (6.3 %). Among men tested, 259/1,635 (15.8 %) had a PV/LPV compared to 2,076/24,120 (8.6 %) women. Of 184 men with breast cancer, 24 (13 %%) had a PV/LPV in the following genes: *BRCA2* (10), *CHEK2* (8), *BRCA1* (2), *PALB2* (2), *ATM* (1), and *TP53* (1). Of 116 men with pancreatic cancer, 17 (14.6 %) had PV/LPV: *BRCA2* (6), *ATM* (4), *BRCA1* (2), *PALB2* (2), *TP53* (2), and *CDKN2A* (1). Among 144 with prostate cancer, 22 had a PV/LPV (15.2 %) and of these 22 men, 17 (77 %) had at least one additional primary cancer: *BRCA2* (7); *CHEK2* (5); *BRCA1* (4); *MSH2* (2); *ATM* (1), *MLH1* (1), *PALB2* (1), and *TP53* (1). Conclusion:In this series, men were nearly twice as likely to have a PV/LPV compared to women. This could be attributed to clinicians using more stringent personal/family history criteria before offering testing to men. Although guidelines have often focused on *BRCA1/2*, 51 % (32/63) of men had a PV/LPV in genes other than *BRCA1/2*. PV/LPV were most commonly identified in *BRCA2*, *CHEK2* and *ATM* in this population. Consideration should be given to genetic testing by inherited cancer panels in men with breast, pancreatic or prostate cancer, particularly in the context of a positive family history.

Characterizing the Clinical Cancer Presentation of Individuals with Pathogenic Variants in NBN

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Background: The NBN protein is a component of the MRN (*MRE11/RAD50/NBN*) complex integral to DNA double strand break repair. Heterozygous pathogenic variants in NBN confer a 3-fold risk for breast cancer and are associated with melanoma, non-Hodgkin lymphoma, and prostate cancer. Our aim was to review the clinical characteristics of patients with pathogenic/likely pathogenic variants (PV/LPV) in NBN. Methods: We retrospectively queried our series of 10,000 Comprehensive and Breast/Ovarian Cancer panels, excluding patients with a PV/LPV in high or moderate risk cancer genes such as *BRCA1/2, ATM, CDH1, CHEK2, PALB2, PTEN, STK11* and *TP53*. Personal and family history was extracted from pedigrees and requisition forms of individuals with a NBN PV/LPV and evaluated against NCCN testing criteria. Results: In this series, 23 patients had a PV/LPV in *NBN*. Of the variants, 16 were frameshift (most often c.657_661del5 (8 patients) and

c.698_701delAACA (3 patients)), 4 splicing, 2 nonsense and one multi-exon deletion. Pedigree review revealed that 21/23 (91 %) mutation carriers had cancer: 17 patients with breast (mean age at diagnosis 48), 3 patients with ovarian (mean age at diagnosis 56) and one patient with colorectal cancer at 52 and basal cell carcinoma. In the series, 20/23 (87 %) met NCCN genetic testing criteria (19 for HBOC, 1 for Lynch). Five patients with breast cancer also reported a second primary cancer (glioblastoma, thyroid, breast, lung, basal cell). All but two patients reported multiple first- and second-degree relatives with cancer such as melanoma, lymphoma and most commonly breast, colon, prostate and pancreatic cancer. Conclusion: The inclusion of *NBN* in multi-gene cancer panels will identify hereditary cancer risk in a small population of patients with breast and ovarian cancer. Factors such as multiple primary cancers and a family history of cancer, especially breast, colon or prostate, increase the likelihood of identifying a PV/LPV in NBN. Patients with a PV/LPV in *NBN* will most often meet NCCN clinical criteria for genetic testing.

Physician Views on Genetic Testing and Cancer Surveillance in Asymptomatic Minors at Risk for Li-Fraumeni Syndrome

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Genetic testing an asymptomatic minor with a parent with Li-Fraumeni syndrome (LFS) has, historically, been controversial due to the lack of universal management recommendations for medical interventions during childhood. Recent guidelines, however, have suggested medical surveillance protocols for children with LFS and ethical guidelines now recognize circumstances in which testing minors may provide psychosocial benefits to families. An online survey targeting oncologists and clinical geneticists, physicians who work in specialties most likely to care for patients with LFS, assessed their (1) experiences with LFS; (2) views regarding testing minors at risk for LFS; (3) perceptions regarding factors which are important to consider prior to testing; and (4) screening recommendations for minors with, or at risk for, LFS. Respondents reported a general lack of experience in working with families with LFS (5.3 % (N = 4) of oncologists and 8.1 % (N = 3) of geneticists had followed more than 10 families with LFS). The majority of respondents (60.5 % (N = 46) of oncologists and 75.7 % (N = 28) of geneticists) reported a high likelihood to test a child when a parent had a *TP53* mutation. Geneticists were more likely than oncologists to view certain factors as important when deciding about genetic testing (such as published surveillance recommendations for children or whether current surveillance regimens would change based on the test result). Interestingly, respondent's recommendations for surveillance were more aggressive for children with a confirmed *TP53* mutation than for those children not tested, but with a parent with a *TP53* mutation. Responses suggest that molecular confirmation of a *TP53* mutation in the child impacts medical management recommendations, which contrasts the standard of treating at risk individuals as positive until proven otherwise. While testing minors at risk for LFS continues to be controversial, physicians are likely to test children despite an observed general lack of knowledge with LFS and screening recommendations inconsistencies.

Assessment of Current Practices in Post-Visit Written Patient Communication Amongst Genetic Counselors

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Providing patients with post-visit written communication is a long-standing tradition in genetic counseling, however characterization of this practice in today's clinical landscape is limited. Our study aimed to characterize the current practice of providing post-visit communications to patients by format, time spent writing and perceived purpose of providing communications following a typical new patient visit. A novel, online mixed methods survey was sent by E-blast to NSGC members. Genetic counselors in clinical practice were asked if they send post-visit communications and if so, which of 7 different types they send and average time spent writing. They were also asked open-ended questions about the perceived purpose for providing written summaries to patients, if/how the practice has changed over time and factors they believed influenced the practice. Eighty three percent (233/280) of respondents reported sending post-visit patient communications. Using pair-wise comparisons by chi-square analysis, we found that the type of communication sent varies based on specialty, with prenatal counselors less likely to send out patient-specific letters or copies of consultation notes than cancer (p=0.010, p=0.048, respectively) or pediatric counselors (p=0.001, p=0.001, respectively). Between-group Bonferroni post-hoc analysis showed that prenatal counselors spend less mean time writing post-visit communications (19.0 min) relative to cancer and pediatric counselors (30.6 min, p=0.027 and 37.7 min, p=0.001, respectively). Using conventional qualitative content analysis, the most commonly cited purpose for sending a post-visit written communication was to provide the patient with a formal account of what was discussed during the visit. Counselors reported that they currently send fewer and shorter patient-specific letters than they did in the past, primarily as a result of having less time due to increased patient volumes. These data suggest post-visit written patient communication practices are variable amongst specialties and are changing as the profession evolves.

V. Counseling/Psychosocial Issues

An Exploration of the Genetic Counselor-Patient Relationship Following a Life-Limiting Prenatal Diagnosis

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The proposed Reciprocal-Engagement Model of genetic counseling is comprised of five core tenets with the relationship between the genetic counselor and patient being central to the process and success of genetic counseling. This study sought to explore the relationship between the genetic counselor and patient during and after a prenatal diagnosis of a "life-limiting" diagnosis that resulted in a major loss (termination, stillbirth/miscarriage, or neonatal death). Eight genetic counselor and patient pairs were individually/separately interviewed about their mutual relationship and asked about the development and maintenance of the relationship, the contributing factors, and the long-term effects on both the genetic counselor and patient. The length of these relationships ranged from 4 months to 14 years following their initiation. All clinical relationships established required extensive follow-up via multiple modes of communication with more frequent communication in the beginning and less as the relationship evolved with more equal initiation of communication over time. The content of conversations expanded to include more personal elements from both the genetic counselor and the patient perspectives. Most participant pairs fell somewhere on a spectrum of professional relationship to deeply personal relationship as one pair maintained an exclusively personal relationship. The support offered by the genetic counselor during the time of crisis was both essential and unique to the patient compared to other healthcare providers and family/friends. Strategies employed and/or characteristics of the genetic counselor and

patient did contribute to the development and maintenance of the relationship as did the life-limiting nature of the diagnosis, which was thought to overall strengthen the connection. The long-term effects on participants reveal clinical implications for genetic counseling. This exploratory study highlights the unique service of support offered by genetic counselors, as well as potential avenues for future research and training implications.

The Effect of Room Environment on Patient Experience in a Prenatal Genetic Counseling Session

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An important facet of aesthetic design, a topic of increasing interest in healthcare, is the concept of using positive distractions to promote wellness. This concept has largely been explored in long-term, inpatient care, and findings suggest these positive distractions decrease patient anxiety. However, little research exists regarding this concept in short term, outpatient care, such as prenatal genetic counseling. This study evaluated the change in anxiety levels from pre- to post-counseling between prenatal genetic counseling patients who were randomly assigned to one of two room environments: an experimental room which incorporated positive distractions, such as a window, plant, art depicting a nature scene, and full-spectrum lighting, or a control room lacking such features. Participants (n=98) were English-speaking patients at a Houston Maternal Fetal Medicine clinic who completed the State-Trait Anxiety Inventory (STAI) pre- and post-genetic counseling and open-ended questions regarding the room environment post-counseling. State anxiety scores decreased in both groups from pre- to post-counseling ($p = 0.011$); however, average changes in anxiety scores from pre- to post-counseling did not differ between the room designs ($p = 0.530$). In addition, patients who chose not to pursue testing or screening post-counseling experienced a greater decrease in anxiety from pre- to post-counseling than those patients who did pursue testing or were undecided ($p = 0.007$). Unlike prior research, these findings suggest the room environment may not significantly impact patient anxiety levels in an outpatient setting. However, these findings may highlight the benefits of genetic counseling in decreasing patient anxiety. Lastly, several themes were identified from responses to open-ended questions, suggesting patients may value certain aesthetic features of clinic rooms, such as having a window.

An Exploration and Analysis of the Reproductive Decision-Making Process in Parents of Children with Wolf-Hirschhorn/4p Deletion Conditions

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Background: Wolf-Hirschhorn syndrome/4p deletion syndrome (WHS/4p-) is characterized by developmental and growth delays, intellectual disabilities, distinctive facial characteristics and seizures. While previous studies have focused on the genetic cause and variation in symptoms, there is a lack of information regarding the effects of this complex etiology and variability. The goal of this study was to explore factors involved in the reproductive decision-making process in parents of children with WHS/4p-. Methods: Members of the 4p- Support Group were recruited for personal interviews and an anonymous online survey. Participants had a biological child with WHS/4p- and were at least 18 years old. Eight parents or parent couples participated in personal interviews and 95 participants completed the survey. Data were analyzed using descriptive statistics and thematic analysis. Results: 61 % of survey participants felt that they had not received balanced information during the initial diagnosis and 47 % did not feel emotionally supported by the medical community. Six of 9 survey participants that were carriers of a balanced translocation agreed that carrier status influenced their reproductive decisions. The most frequently utilized reproductive option among survey respondents in subsequent pregnancies was prenatal diagnosis via amniocentesis or chorionic villus sampling (21 %); the majority did not consider pregnancy termination. Emotional burden of care was reported to be more significant than financial burden of care. Parental perception of severity of child's phenotype and religious beliefs did not appear to influence decision making. The majority agreed that having a sibling, either typically developing or with WHS/4p-, would benefit other sibling(s). Discussion: Reproductive decision-making is a complex process in the WHS/4p-community. Many families reported a desire for more emotional support from healthcare providers and balanced information at diagnosis. Future studies can expand upon reproductive decision-making of balanced translocation carriers or fathers.

Telling the Truth About Turner Syndrome: Disclosure of a Diagnosis and Infertility to a Romantic Partner

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Women with Turner syndrome (TS) often struggle with shyness, social anxiety, and low self-esteem, and as a result, may have trouble forming romantic relationships. Studies have identified concerns about infertility as a primary issue for women with TS. Little research however, has looked at how women discuss their diagnosis of TS and infertility with others and none exists that has focused specifically on disclosure to romantic partners. The purpose of this study was to explore the experiences of women who disclosed their diagnosis of TS and infertility to romantic partners. We performed semi-structured interviews with 10 women recruited through the Turner Syndrome Society of the United States, Turner Syndrome Support Group of Boston and by word of mouth. Questions focused on life with TS and infertility, disclosure to romantic partners, and advice for others. We coded and analyzed interview transcripts, using ATLAS.ti software, and identified emergent themes. The women in our study ranged in age from 23 to 38 years and the number of partners they had varied from one to ten. Participants emphasized the importance of a strong sense of self, and those who were confident and accepting of TS typically had more positive disclosure experiences. Often, their confidence came from supportive parents, yet regardless of upbringing, all felt that infertility caused isolation. Participants perceived a benefit to being in control of disclosure conversations and felt that discussions with romantic partners present unique challenges, due to issues surrounding having children, and the impact the condition has on a partner. Advice to others with TS included seeking guidance from women who have previously disclosed to partners, disclosing in a comfortable manner, being proud of yourself, and creating a strong support network. Future studies should focus on partners' perspectives to gain additional insight on how women with TS can best have these discussions.

The Impact of Online Images of Neurofibromatosis Type 1 on the Parents of Newly Diagnosed Children

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Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with a *de novo* rate of 50 %. As a result, many affected children are born to parents with no prior knowledge of NF1. Internet searches for information about NF1 typically uncover pictures depicting the most severe end of the disease spectrum. Therefore, parents encountering these images may not get an accurate representation of what the disorder means for their child. This study aimed to gather insights from parents of children with a new diagnosis of NF1 and no prior knowledge of the disease who viewed internet images of affected individuals. We performed semi-structured interviews with seven mothers recruited from the Children's Tumor Foundations NF Registry. Discussions focused on diagnostic stories, first encounters with internet images of NF1, sharing of pictures with other individuals and advice for future parents of children with NF1. Participants ranged in age from 30 to 40 years and their children were between 2 and 3 years old. Mothers felt parents should be advocates for their children when a medical concern arises, with four proactively seeking out NF1 information online. Viewing internet images caused every participant to have negative feelings such as worry or heartbreak. Mothers also felt that online photos misrepresent their child's diagnosis and the NF1 population as a whole and that the most memorable images represented very severe cases of NF1. All participants viewed sharing NF1 images with friends or family as a personal choice, and felt they would introduce images to their children at an appropriate time when they were older. Advice for future parents of children with NF1 included seeking information from reputable sources and being aware that NF1 is not usually as severe as the images online. Future studies should focus on a larger sample size that includes fathers, parents of older or more severely affected children and individuals with varying levels of health literacy, to gain broader insights about the effects of viewing NF1 images on the internet.

Secondary Finding Preferences in Whole Genome Sequencing: Experiences with a Large Developmental Delay Cohort

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Developmental delay, intellectual disability, and related congenital defects (DD/ID) affect ~1–2 % of children born and have a large impact on affected individuals and their families. Though many cases are attributed to an underlying genetic cause, identification of the specific variation often proves elusive. As part of the Clinical Sequencing Exploratory Research Consortium, we are conducting whole exome/genome sequencing in ~450 affected probands and their parents to establish a genetic diagnosis for DD/ID and better understand the utility and impact of large scale sequencing in a pediatric neurology clinic. To date, we have enrolled 210 families, and have completed sequencing and analysis for 123. We have successfully identified DD/ID pathogenic or likely pathogenic variants in ~25 % of our probands and have identified potentially pathogenic secondary findings in ~10 % of parent participants. Participants are randomized to provide preferences for secondary finding disclosure either at time of study enrollment or at result return. Preferences are gathered through a novel instrument developed to illicit preferences on the types of risk information an individual would like to receive with categories defined by disease type (diabetes, cancer, alzheimer's disease). When pathogenic variants are identified, these preferences are used to determine whether a result is returned. Analysis of preferences solicited to date show that the overwhelming majority (>80 %) of parents in this study elect to receive all types of secondary findings. However a minority of parents elects not to receive one or more categories of results. The categories declined vary with the most common category declined being risk of developing obesity. Reasons for decline include a lack of interest, perception of low risk status, or anxiety surrounding a specific category or type of disease. Reported secondary findings to date include genetic variation leading to an increased risk for malignant hyperthermia, cancer, and heart disease as well as carrier status for select recessive diseases.

Assessing the Perception of Fertility Preservation Within the Turner Syndrome Community

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Background: Turner syndrome (TS) is the most common sex chromosome disorder. A hallmark clinical feature of TS is early ovarian failure, which severely decreases a woman's chances of achieving natural pregnancy. Ovarian tissue cryopreservation (OTC), an experimental fertility preservation process, may provide women with TS another reproductive option. This study explored the attitudes of the Turner syndrome community regarding possible issues surrounding fertility preservation. Methods: Each individual participated in one semi-structured phone interview. The interview was developed using grounded theory and was based on the current reproductive issues in TS. Participants were asked to reflect on their attitudes and possible experiences with infertility as well as their interest in fertility preservation. Interviews were audio recorded and transcribed; responses were coded and categorized into higher order themes. Results: Eleven participants were interviewed. The issue of infertility was an emotional burden for most, which was not always adequately addressed by doctors. Participants also expressed desire for a woman with TS to have her own biological children. Participants had considered alternative reproductive options, namely adoption. Reactions to experimental fertility preservation by OTC were mainly positive, but there were some concerns about the surgery. Some parents believed the daughter should autonomously make the decision whether to undergo the process once she is of adult age. Conclusions: Literature supports families' desire to have personalized, in-depth discussions on fertility (options); genetic counselors can help meet this need. A pediatric genetic counselor can discuss reproductive options with families of girls with TS before it is too late to preserve fertility. By understanding the experiences of parents and women living with TS that create the psychosocial issues surrounding reproductive issues, clinicians can better anticipate and appreciate how the TS community will respond to the prospect of experimental fertility preservation.

Impact of Huntington's Disease Gene Positive Status on the Lives of Presymptomatic Young Adults and Recommendations for Genetic Counselors

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Introduction: Predictive testing for Huntington's disease (HD) has been available for over 20 years to asymptomatic at-risk individuals. Young adults (<=35 years old) make up approximately half of the population who has undergone predictive testing. Studies targeting young adults' predictive testing experiences have focused on the time period immediately surrounding testing. Little is known about the long-term impact of being gene positive. Purpose: We aimed to explore how the knowledge of HD gene positive status influences various aspects (career and education, romantic relationships, family planning, etc.) of the lives of presymptomatic young adults, and young adults' experiences with the predictive testing process and suggestions for genetic counselors. Methods: Adults <= 35 years who had tested positive for >= 6 months were recruited via support groups, HD Society of America National Youth Alliance, and HD Youth Organization. Participants (N=14) completed a semi-structured interview via telephone or Internet. An iterative coding process was used to identify major themes. Results: (1) Knowing one's gene positive status helped participants "mature faster" and "become better people". Greater appreciation of time led to clearer priorities for life, living in the moment and letting go of trivial worries. Participants planned to obtain career and family planning goals faster due to limited healthy years. (2) Concerns included fears and experiences of discrimination, loneliness, and uncertainty about how much to disclose about gene positive status in personal relationships. (3) Some appreciated the pre-test counseling process whereas others saw it as a hurdle. Many expressed appreciation or desire for a follow-up plan. Conclusions: Results demonstrate that young adults are well equipped to handle a positive result. Opportunities exist for genetic counselors to more carefully address young adults' concerns identified in this study. In the future, ways to make the predictive testing process more concise and accessible with follow-up plans in place should be considered.

Does a Negative Prenatal Genetic Screen Result Impact Maternal-Fetal Bonding?

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Background: The maternal-fetal bond (MFB) is the affectionate relationship between mother and fetus. There is a little evidence suggesting that prenatal screening for fetal aneuploidy – regardless of result –may have a negative impact on MFB. Given the rapidly increasing options available for prenatal genetic screening, it is crucial to improve our understanding of the impact of these tests on MFB. Purpose: To explore the impact of negative prenatal genetic screening results on MFB. Methods: Women were recruited from healthcare providers' offices and community events to participate in semi-structured (45–60 minute) interviews in person or by telephone. Data analysis informed data collection using the constant comparative method. Interviews were recorded and transcribed verbatim. Constructivist grounded theory was used in data coding to generate categories and a cohesive theoretical model. Reflexive journaling and peer debriefing were used to enhance credibility, confirmability, and dependability of results. Results and Discussion: Interviews were conducted until saturation was reached (N=9). Participants (mean age: 32.78) all conceived naturally, had a romantic partner, and received care from a variety of prenatal providers. This was a planned pregnancy for seven women (78 %), and first pregnancy for five (56 %). Four women had noninvasive prenatal testing (NIPT) and five had maternal serum screening. Women described an instant instinct to protect (Theme 1) and saw bonding as imagining life with a baby (Theme 2). For women who trust their gut (Theme 3), genetic screening didn't impact MFB, but for women who felt the need for information and saw planning as love (Theme 4), genetic screening was a time for holding their breath (Theme 5), and a negative result brought a sigh of relief (Theme 6) and let them give themselves permission to relax into the pregnancy (Theme 7) and connect more deeply. Findings from this study provide insight into patients' experiences that can enhance clinicians' ability to empathize with and empower patients as they engage in prenatal testing for fetal aneuploidy.

Conception Through Gamete Donation: Unique Counseling Considerations in the Era of Genome-Wide Testing

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Individuals conceived through egg, embryo, and sperm donation are increasingly and openly presenting for medical care in the United States. Their methods of conception present unique counseling issues when these individuals present for genetic evaluation and the use of genome-wide technology is considered. Triad testing when ordering genome-wide tests, including chromosomal microarray (CMA) or whole genome/exome sequencing (WGS/WES), on a donor-conceived proband is complex. Genetic counselors who are involved in evaluation and testing of these individuals need to be familiar with the current trends in assisted reproductive technologies so that they can accurately educate these patient populations to aid in the decision-making process and achieve informed consent. Failure to consider these circumstances and limitations of testing can lead to patient distress and poor outcomes. The following counseling considerations will be described: (1) Donor-conceived individuals are openly presenting for genetic evaluation in an increasing number of medical settings and genetic counselors and other healthcare providers need to be prepared for appropriately managing their care. The use of donor gametes is more frequently disclosed to healthcare providers than in previous generations due to shifts in recipient populations and greater openness and acceptability of these practices in society. (2) The gamete donor facility may decline to facilitate testing or be unable to accommodate requests due to the limited scope of services offered by these organizations. (3) The donor may be unavailable for testing. (4) Interpretation of a variant of unknown clinical significance or an incidental finding is complex when many healthy offspring exist from that donor. Counseling should establish the family's understanding of the benefits and limitations of these testing options as well as the potential for complex outcomes.

The Patient Experience Matters: Emotional Reactions to Expanded Carrier Screening

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Introduction: Expanded carrier screening (ECS) is now routinely used in the clinical setting for patients planning or early in pregnancy. To date, no study has investigated patients' reactions to ECS. We aimed to understand patients' perceived utility of expanded carrier screening results. Our initial analysis focused on how patients identified as carriers vs. non-carriers for included diseases felt about their screening results. Methods: Patients receiving ECS through a laboratory were sent a survey approximately 3 weeks after results were returned. The survey included a modified version of the validated "REVEAL Impact of Genetic Testing in Alzheimer's Disease" measure, recommended for use in monitoring patients who receive genetic information. Results from this measure were analyzed and compared between carriers vs. non-carriers. Consent was obtained for all participants. Results: A total of 76 participants completed the survey. Carriers and non-carriers reported a significant difference between how often they felt the following: sad (p=0.0092), surprised

(p=0.038), and anxious (p=0.0011) regarding their results and worried about their children developing disease (p=0.045). Carriers and non-carriers did not report a significant difference (p>0.05) between how often they felt the following: relief, happiness, loss of control and regret. Discussion: As expected, carriers and non-carriers had different feelings towards their results. Carriers more often felt anxious and worried about their results. Interestingly, carriers did not feel relief or happiness about their results less often than non-carriers, though this may be the result of post-test genetic counseling provided. This highlights the importance of genetic counseling. Our results also show that 90 % of patients reported they did not feel regret regarding their results. This data suggests that expanded carrier screening is not detrimental to patients. Analyses of other measures such as impact on decision-making and communication about results are necessary to fully evaluate perceived utility.

The Importance of Social Support in the Undiagnosed Diseases Community

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Previous work related to parental uncertainty has highlighted the importance of social aspects of uncertainty; identifying parents in similar situations who can offer empathic support. The purpose of this analysis was to explore the social uncertainty perceived by parents of children with undiagnosed medical conditions. Parents were recruited through online support groups to complete a cross-sectional, mixed methods study exploring the domains of uncertainty. The current analysis was conducted on the qualitative data from 96 parents' responses on perceptions of uncertainty. Responses were coded and analyzed looking for common themes by two investigators with close agreement; residual discrepancies were reconciled. Many parents conveyed the challenges in finding support through other parents leaving them without a sense of community. They also described feeling a lack of understanding from those who did not share similar parenting experiences. Parents further discussed social uncertainty including strong feelings of isolation, the need for validation of their concerns, and feeling as though they lacked the words to describe their experiences and their child to others, including medical professionals. One parent stated that uncertainty has caused the "loss of friendships and relationships because people don't understand and you can't make them understand". Another explained, "I don't feel like I can explain what's happening to medical professionals or that they always believe me". Lacking the words to describe your child and feeling ignored by medical professionals are likely to exacerbate feelings of isolation and impede adaptation. Genetic counselors are in a unique position to help families mitigate aspects of social uncertainty by identifying potential sources of social support and providing families with easily understood vocabulary about their child's condition. This study contributes to our understanding of uncertainty and its broad effects on parents. It also identifies an opportunity for genetic counselors to use their skills to promote healthy adaptation.

Genetics Education and Counseling of Incarcerated Women: Beginning the Conversation

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Genetic counselors periodically see incarcerated patients. However, there is virtually no research on genetic counseling in this population. This research was intended to initiate a conversation on the genetic counseling of incarcerated women. It was also designed to assess the effectiveness of different techniques that genetic counselors may use to better reach their incarcerated patients. Six guest lectures on the science and ethics of human genetics were prepared and delivered to a select group of 19 students in the Bedford Hills College Program at the Bedford Hills Correctional Facility for women in Bedford Hills, New York. Vocabulary lists and visual aids were distributed for each lecture. Each lecture was analyzed for its effectiveness and impact. Additionally, 12 participating students were administered a course evaluation wherein they shared their thoughts on the lectures and handouts. The student inmates' responses suggested that prenatal genetics issues, such as age-related risks during pregnancy, were most relevant and valuable to them. Three respondents specifically indicated that they are planning to conceive upon release from prison. Additionally, the information gleaned through a review of the literature, the participants' responses, and the lecture series itself identified key issues to address as genetic counselors attempt to better serve incarcerated patients. The students who participated in this lecture series benefited from simple explanations and visual aids, as would most genetic counseling patients, incarcerated or not. They also expressed significant distrust of the medical system. Results show that genetic counselors should strive to build rapport with incarcerated patients, use visual aids, and be prepared to address sensitive subjects such as substance abuse, domestic violence, and mental illness with them. Furthermore, educating more incarcerated women about genetics may help them establish more faith in genetic counseling as a valuable health service.

Experiences with Whole Exome Sequencing

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Whole exome sequencing (WES) is a complex genomic test involving sequencing of the protein-coding regions of the genome. Interpreting and reporting WES results involves complex counseling, medical and ethical issues. This qualitative study explored parental perspectives on the process of WES; assessed parental knowledge and understanding of their child's WES results in comparison to the WES laboratory report and genetics evaluation; and analyzed the similarities and differences between the parents' and clinicians' perspectives regarding the WES process. Most previous WES research has centered on discovering genetic causes for disease and professional opinions. There has been limited research on perspectives of patients and families undergoing clinical WES. Four families were interviewed, along with a corresponding chart review of WES documents, and interviews with the genetics providers involved. A collective case study methodology was utilized, which involved in-depth description and analysis of the application of WES with triangulating data from multiple sources - parents, genetics professionals and laboratory data. Following the collective case study approach, four cases were individually assessed followed by a between-case analysis. Major themes included a "motivation to end the diagnostic odyssey" as the primary reason to pursue WES for both parents and genetics professionals; "learning through genetic testing" as parents described their experiences with previous genetic testing as having helped them to learn to cope with stress and uncertainty in WES; "valuing simplicity and honestly in WES counseling" was important for both parents and genetic professionals; "returning results in person" was essential to the parents' understanding of the test results; and parents felt empowered by the support from genetics professionals. This study adds rich description to the WES process. Moreover, it highlights the importance and necessity of thorough and

transparent genetic counseling and its ability to empower patients regardless of WES outcome.

Family History: Separating Truth from Fiction. Cancer Risk Assessment's Unique Vulnerability to Munchhausen Syndrome

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Taking a medical and family history is an integral part of a Cancer Risk Assessment (CRA). CRA is one of the few areas of medicine in which a person may have a surgical procedure, with significant risks, without any diagnostic test. Through a real life case scenario, I came face to face with the reality of Munchhausen syndrome and my responsibility to "do no harm" as a genetic counselor. Upon reflection and with a thorough review of the literature, I developed an original scale from which genetic counselors can assess the client's family "story". This original continuum (truth, misinformation, misunderstanding, misrepresentation, to lying) will be thoroughly explored and applied to an illustrative case. An individual's perception of risk is also an integral part of their family "story". Utilizing a framework of a comprehensive literature review, the factitious disorder (aka Munchhausen syndrome) will be explored. The perception of one's risk and the seeking of attention are vastly different. However, in this discussion one will see how they overlap and conflict. Finally, the Genetic Counseling Code of Ethics will be examined with respect to the responsibilities of a genetic counselor: to myself, to my client, to my colleagues, and to society. This lecture is sure to raise many ethical questions and a framework from which to debate Cancer Risk Assessment's unique vulnerability to Munchhausen Syndrome.

Patients' Opinions on Genetic Counseling on the Increased Risk of Parkinson's Disease Among Gaucher Disease Carriers

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Carrier screening for Gaucher disease (GD) is routinely offered to couples during or prior to pregnancy. Carriers for GD have been found to have an increased lifetime risk of developing Parkinson's disease (PD); however, patients are not generally informed about this increased risk. This study aims to determine if patients prefer to learn about this correlation and if learning this information would affect carrier screening uptake, and to characterize the potential psychological impact of learning this information. A survey was administered to individuals who screened negative for GD. Of the 75 participants, 86.7 % indicated that everyone should be informed about the increased risk of PD prior to having GD carrier screening, and 93.3 % responded that they would still have had carrier screening had they received this information beforehand. These results indicate that healthcare providers should counsel patients on this topic in order to align care with patient preferences.

Parents' Experience Having a Child Diagnosed with more than One Genetic Disorder

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While the effect of having a child diagnosed with a single genetic disorder has been extensively studied, to our knowledge, no published studies have described the psychosocial impact that having a child diagnosed with co-occurring, yet unrelated, genetic disorders has on parents. In the presented study, semi-structured interviews were conducted with four mothers and one father of children diagnosed with two distinct genetic disorders. These interviews explored the experiences of the parents and the challenges that arise as a result of this unique situation. Interview transcripts were analyzed using the qualitative method of interpretative phenomenological analysis. Results indicated that these parents share some experiences similar to those previously reported by parents of children with a single genetic condition, such as emotions around the diagnosis, impact on relationships with family and friends and changes in values and view on life. However, the findings also elicited some novel experiences and challenges faced by these families. The challenges included frustration toward health care providers who dismissed parents' input on the effective management of their child's two conditions, delay in the diagnosis of the second condition due to misattribution of additional symptoms to the first diagnosis and difficulty balancing the medical management of two seemingly distinct conditions. These findings suggest that healthcare providers should encourage greater collaborative involvement of parents in the care of their child, as there are significant challenges in managing two conditions. Additionally, parents may be more of the expert in this unique situation due to their intimate and extensive experience caring for their ill child as compared to the providers' limited expertise on the combination of rare genetic disorders. Sharing the experiences of parents raising a child with multiple unrelated genetic disorders may help to provide guidance for healthcare professionals to better understand and effectively address some of the unique issues faced by these families.

Parental Disclosure of Familial Amyotrophic Lateral Sclerosis Diagnosis and Mutation Status to Children: Perceptions of Young-Adult Offspring

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Background: This qualitative study examined parents' communication with their children about the diagnosis of amyotrophic lateral sclerosis (ALS) and the genetic component of the disease, and to explore if there was a relationship between the disclosure experience and decision-making about genetic testing options. Methods: We spoke with 8 individuals utilizing a semi-structured interview. Participants had a parent with an *SOD1* or *C9orf72* familial ALS (FALS) mutation, and were ages 20–33 years. Interviews attempted to identify whether timing and content of disclosure of parental FALS influences the outlook of young adult offspring on FALS genetic testing. Results: Participants were most likely to prefer open honest communication during the disclosure process, but they also acknowledged that everything changes the moment the diagnosis is disclosed and that "ignorance is bliss." Communication was dictated by disease awareness within the family. Participants each had a unique experience with the presence of ALS in their lives once the diagnosis was made; yet this was often tied to a sense of loss of control of their own futures. Most participants referred to a duty to protect their family from the emotional pain and anxiety experienced from the knowledge of the diagnosis. Conclusion: Opinions about testing were determined by wanting to gain back control over their lives, or an avoidance of the stress testing would cause them. In conclusion, information obtained from this study may help genetic counselors guide their patients in the disclosure

process and assist at-risk young adult family members during the genetic testing decision-making process.

Paternal Adaptation to a Child's Diagnosis of Fragile X Syndrome: Predictors of Individual and Family Well-Being

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A family's ability to positively adapt to a child's diagnosis of Fragile X Syndrome (FXS) depends on individual family members' resilience. Previous work on adaptation in FXS families has predominately focused on mothers. Few have studied fathers' resilience and contributions to family well-being, the focus of this research. We explored predictors of personal well-being and family quality of life (FQoL) from a paternal perspective. An online survey using validated measures of coping strategies (problem & emotion-focused), relationship satisfaction, parenting stress, family communication, personal well-being, and FQoL (i.e., Family Interaction, Parenting Satisfaction, Emotional Well-Being, Physical/Material Well-Being, Disability Support) was distributed nationally via support groups to fathers of children with FXS (N=110). We used hierarchical linear regressions to assess predictors of personal well-being and subscales of FQoL. The three predictors blocks were: 1) family environment (income, education, number of affected children), 2) fathers' personal attributes (coping styles, perceived FXS knowledge, perceived severity of child symptoms), and 3) family dynamics (marital satisfaction, parenting stress). While personal well-being and FQoL were significantly correlated (r=.20, p=.03), different variables predicted these outcomes. Problem-focused coping and parenting stress significantly predicted fathers' personal well-being (p<.01). Relationship satisfaction and parenting stress were significant predictors for 3 of 5 FQoL subscales (Family Interaction, Parenting Satisfaction, Emotional Well-being) (p<.01). Our findings show that paternal coping strategies in FXS families differ from previously-reported, maternal emotion-focused approaches and also suggest that the partnership between spouses is important for positive family adaptation. Genetic counselors should consider gender differences in individual adaptation, work to engage fathers in sessions (especially by bolstering marital partnerships), and consider a family-centered counseling approach.

Social Connections in Families with Li-Fraumeni Syndrome: A Preliminary Report

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Introduction and Purpose: Li-Fraumeni Syndrome (LFS) is a rare inherited disorder with the only known cause being germline mutations in the TP53 gene. Mutation carriers have an exceedingly high (>90 %) lifetime chance of developing one or more malignancies. Although there are multiple publications of assessment of psychological status of families with hereditary cancer predispositions such as LFS, there are few examples of social assessments. This study presents findings of a mixed method study for the purpose of filling this knowledge gap by describing the role of friends and spirituality/religiosity in easing the burden of families with LFS. Methods: We evaluated 66 members of LFS families attending National Cancer Institute LFS Study clinic at the National Institues of Health Clinical Center between 2011 and 2015. During the first clinical visit we assessed distress with the BSI-18, and several types of social exchanges among the study participants using an established interactive research tool called the Colored Eco-Genetic Relationship Map (CEGRM). We performed both quantitative and qualitative analyses of social relationships with LFS family members and close non-kin. Results: Of the 59 BSI-18 Distress measures completed by adult participants, the Global Symptom Inventory mean was 46, i.e., low-normal, with a few outliers at +/− 1 standard deviation. Anxiety, depression and somatization sub-scale means were similar. We found that reported friendships varied widely in number and type, that the friendships were often deep and enduring, and were important sources of informational, tangible, emotional and spiritual support. Confidantes tended to be best friends and/or spouses. Organized religion was important in selected families, typically from mainstream traditions. However, a number of other people identified themselves as "spiritual-but-not-religious" and reported spiritual and humanist explorations. Conclusions: Our results shed preliminary light on how people in families with LFS cope in the face of overwhelming medical, social and emotional challenges.

Prenatal Genetic Testing and Screening for Consanguineous Couples: Is Clinical Practice Consistent with Practice Guidelines?

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Our study assessed the preconception and prenatal genetic counseling services offered to consanguineous couples in North America. We surveyed prenatal genetic counselors who have worked in a prenatal setting at any point between the years 2010 and 2015. Our online survey contained both quantitative and qualitative questions and we received 132 completed surveys. We analyzed quantitative responses using Statistical Package for the Social Sciences (version 22) and used thematic network analysis to identify common themes in open-ended responses. Respondents in our study had an average of 7.5 years of experience in a prenatal setting and they have counseled an average of 19 consanguineous couples since the start of their career. The mean baseline risk respondents quoted for consanguineous couples to have a child with a genetic disorder or congenital anomaly ranged from 5.02 to 10.55 % depending on the degree of relatedness while counselors cited a 3.57 % mean baseline risk for unrelated couples. The common psychosocial concerns perceived by respondents when counseling consanguineous couples were stigma, discrimination, fear, and blame as well as some arising from a couple's cultural and religious beliefs. Fifty-four percent of counselors reported that they refer to some guideline, the majority referring to the NSGC guideline for genetic counseling and screening of consanguineous couples and their offspring, published in 2002. When asked if they have recommendations for revising the NSGC guidelines, a number of respondents suggested they be revised to include information on offering new technologies such as expanded carrier screening, noninvasive prenatal testing (NIPT), chromosomal microarray and exome sequencing to consanguineous couples and their offspring as well as strategies for discussing incidental/secondary findings with consanguineous couples. This study, although limited in size, demonstrates that the genetic counseling practices for consanguineous couples is more consistent than observed in the previous study in 1999.

The Role of Counseling in Facilitating Parent–Child Communication about Genetic Breast Cancer Risk

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Women at genetic risk for breast cancer are urged to tell their adult relatives about cancer-causing mutations in the family. In the case of *BRCA1/2*, informing relatives can be lifesaving. High risk women often collaborate with their genetic counselors to follow this advice. However, women may also want to tell their minor-age offspring about BRCA in the family, despite the lack of medical implications in childhood. There is very little empirical data to gauge how commonly these issues are or are not raised during genetic counseling sessions, or ways to support family communication about cancer risk with young people. As part of a multi-site randomized controlled trial, we conducted post-genetic counseling debriefing interviews (separately with counseled women and their counselors) to ascertain the frequency of how often women (N=231) and/or counselors addressed issues in-session pertaining to BRCA and childrearing. In the majority of coded counseling episodes (N=356), discussions between women and counselors about disclosing BRCA test results to children were fairly common (54–85 %), including discussion of pediatric BRCA testing (32–64 %). In 77 % of sessions overall, and 88 % of sessions among BRCA+ women only, women requested more information about communicating genetic breast cancer risk information to their children: women were also 4.7x more likely to ask counselors for support in talking with children about BRCA than counselors were to recognize this need in their own clients, X2(1)=16.9, p<.001. After genetic counseling, we queried women about what specific resources were needed to help them make more informed choices about communicating BRCA risk information to their offspring: 83 % desired a decision guide, 83 % wanted convenient access to an interactive experience (i.e., telephone conversation), and 79 % wanted peer support/connection with experienced BRCA previvor/survivor. Our data highlight key interactions between women and genetic counselors about BRCA and childrearing, and insights into supporting open parent–child communication about genetic breast cancer risk in families.

From Projection to Empathy: Characterizing Genetic Counselors' Countertransference Experiences

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Introduction: Countertransference (CT) refers to conscious and unconscious emotions, fantasies, behaviors, perceptions, and psychological defenses genetic counselors experience in response to any aspect of genetic counseling situations (Weil). Some authors discuss the importance of recognizing and managing CT, but no studies have explored genetic counselors' experiences of CT. This study investigated how clinical genetic counselors define CT, the nature of their CT experiences, and their strategies to effectively manage CT. Method: An anonymous online survey, sent to NSGC members yielded usable data for 142 participants. Participants indicated agreement with the provided definition of CT and completed 28 Likert-type items rating their CT propensities (1=Little/not characteristic, 4= Very characteristic); 57 participants also provided examples of CT they experienced in their practice. Results: A large majority agreed with the CT definition (88.85 %). Factor analysis of CT items yielded four factors: Control, Conflict Avoidance, Directiveness, and Self-Regulation, accounting for 38.5 % of response variance. Thematic analysis of CT examples yielded common triggers: general similarity to the patient, medical/genetic similarity, angry patients, patient behaves differently from counselor expectations, and disclosing bad news. Common manifestations were: being self-focused, projecting feelings onto the patient, intense emotional reaction to patient, overly invested, disengaged, and physical reaction. CT Effects were: empathic break, increased empathy, boundary crossing, conversation does not reach fullest potential, and counselor is drained emotionally. Management strategies were: recognizing CT as it occurs, self-reflection, and consultation. Conclusion: Genetic counselors experience CT for various reasons and CT can manifest in different ways. Training programs, continuing education, and peer supervision might include discussion of CT, informed by examples from this study, to increase genetic counselor skills for managing this phenomenon with patients.

Understanding Psychosocial Outcomes Among Couples Affected by Genetic Breast Cancer Risk: Counseling Implications

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Over 1M women have undergone genetic testing for *BRCA1/2* mutations–which carry an 85 % lifetime risk of breast cancer. Although this genetic test is essential to help women make more informed decisions to protect their health, genetic discoveries far outpace the programs and services that are available to aid these women and their spouses/partners ("partners") to manage the uncertainty of familial risk of breast cancer together. This includes managing the psychosocial toll on each of them as individuals, but also as a couple/family. Women with *BRCA1/2* mutations and their partners face high uncertainty and stress about this substantial cancer threat, yet lack tailored resources to collaborate together to confront multiple, complex treatment decisions. Genetic counselors are appropriate sources of patients' short-term support, but partners are the main source of enduring support and shared decision making. Because we recognize that partners cannot effectively perform this role without adequate preparation, the purpose of this session is to inform the genetic counseling community about the state-of-the-science in understanding psychosocial outcomes among couples affected by genetic breast cancer risk. We will do so by providing a clinical rationale for focusing on couple-level outcomes, define them and describe their typology, and review existing evidence generated from empirical studies in this area of work. Where appropriate, we will address core principles of couples-focused intervention, metrics of successful engagement, and challenges encountered in clinical settings and outcomes research/lessons learned addressing this topic. Specifically, we will cover partners' need for access to genetic information, stress management and coping skills, and ways to communicate openly and compassionately with women facing genetic breast cancer threats and diagnoses. This evidence base includes our own work and the works of others on the development, implementation, and evaluation of counseling support services and resources.

Life with a Primary Immunodeficiency

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Purpose: There are over 250 known genetic immune disorders, yet the subspecialty remains relatively uncharted territory for genetic counselors. In order to better understand the challenges faced by these families and special opportunities for genetic counselors and other allied health providers working in this area, a systematic review of research on psychosocial dimensions of primary immune disorders was conducted. Methods: A systematic review was conducted via PubMed and Scopus to include original research on psychological, social, or behavioral aspects of illness published between 1999 and 2015. A Title/Abstract search was conducted using disease specific keywords (for example: "primary immune deficiency" OR "common variable immune deficiency" AND "psychosocial" OR "quality of life" etc.). The resulting 225 candidate article abstracts were manually reviewed, forward/backward reference searches were completed, and findings were synthesized. Results: Twenty-nine studies met inclusion criteria. Half of the studies focused on mixed primary immunodeficiency, primary antibody deficiency or common variable immune deficiency patient populations; the remaining studies focused more specifically on patient populations such as X-linked agammaglobulinemia, severe combined immune deficiency, etc. The studies illuminate themes such as the potential for negative psychosocial impact from disease; adaptation over time; the complex assessments of quality of life; familial impact; the important roles of hope, developing a sense of control, social support; and addressing anxiety/depression in our patients and their families. Methodological considerations (e.g., parent proxy- vs. child self-report) and areas for improvement are discussed. Conclusion: We propose the research agenda focus on study creativity and rigor, with improved engagement with existing empirical and theoretical literature and critical study design (e.g., methodology with adequate statistical power, creative variable selection, etc.). Additionally, we highlight special clinical and research opportunities.

VI. Education

The Relationship Between the Supervisor Role and Compassion Fatigue and Burnout in Genetic Counseling

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The majority of genetic counselors provide supervision to students at some point during their career. Previous studies have shown that genetic counselors, in general, are at moderate to high risk for compassion fatigue and that certain factors such as inherent anxiety increase this risk. However, no studies have explored the relationship between job duties such as supervision and the development of compassion fatigue and burnout in genetic counselors. The purpose of this study was to determine if there was a difference in compassion fatigue and burnout levels in genetic counselors who supervise compared to genetic counselors who do not. Genetic counselors who currently practice in a clinical setting (N=391) completed an online survey containing demographic questions, the Professional Quality of Life Scale, the State-Trait Anxiety Inventory, and questions specific to the genetic counselor's experiences with supervision. Results indicated that genetic counseling supervisors had significantly lower levels of compassion satisfaction as compared to non-supervisors (p=0.026). However, no difference was found between the two groups when controlling for levels of trait anxiety. Within supervisors, those with more supervision experience reported less secondary traumatic stress. Those supervisors reporting greater confidence in supervision roles had increased compassion satisfaction and decreased burnout and secondary traumatic stress. The findings of this study indicate that there is no difference in burnout or compassion fatigue between supervisors and non-supervisors when controlling for anxiety. However, less experience or less confidence in their supervision role were related to burnout and compassion fatigue among supervisors. Therefore, we recommend training in supervision and support for dealing with compassion fatigue and burnout for supervisors with less experience and less confidence in their role as a supervisor.

Training Methods for Delivering Difficult News in Genetic Counseling and Genetics Residency Training Programs

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Introduction: Genetic counselors and geneticists are often in the position of delivering difficult news (DDN) to patients. Many studies state that healthcare providers need to improve DDN in a manner that is satisfactory to their patients. The purpose of this study was to assess the amount and methodology of DDN training received by genetic counselors and geneticists in their training programs. Hypothesis: We hypothesize that genetic counseling (GC) programs utilize multiple effective methods in training students to deliver difficult news and that they utilize more strategies than genetics residency programs. Methods: We invited all GC and genetics residency program directors to participate in an online survey assessing coursework and clinical experiences dedicated to teaching DDN. Results: Eight-five percent of GC program directors and 26 % of genetic residency program directors completed the survey. GC and genetic residency directors unanimously agreed it is important for genetic counselors and geneticists to be able to deliver difficult news effectively. They agreed that training programs should include formal instruction on this important skill. The majority (75 %) of GC programs employed a wide variety of teaching methods including role plays, reviewing articles, and attending lectures while most genetics residency programs used only two common training methods. Seventy-eight percent of genetic counseling program directors and 93 % of genetics residency program directors agree there should be recommendations for how to teach students to deliver difficult news. Conclusions: Our results show that techniques for DDN are integrated more fully into GC program curricula than genetics residency curricula. Both groups of program directors agree that DDN is an important aspect of student training and as a result, desire standardized recommendations for training students to deliver difficult news effectively.

Exploring Communication Patterns in the Discussion of Maternal Phenylketonuria Syndrome Between Parents and Daughters

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Maternal phenylketonuria (PKU) syndrome is the collection of features and birth defects that arise from uncontrolled phenylalanine levels in a pregnant woman with phenylalanine hydroxylase (PAH) deficiency, previously known as phenylketonuria. Currently, the literature is lacking in exploring what young women are being told about maternal PKU syndrome. In this study, communication patterns between parents and their daughters about maternal PKU syndrome were investigated through an online survey completed by parents. The survey assessed parents' level of comfort with this topic, the information they discussed with their daughter and the resources they accessed. Follow-up interviews were conducted with participants to elaborate on survey responses. The majority of participants were very comfortable discussing maternal PKU syndrome

(51 %); however, 21 % reported being very uncomfortable with the discussion. Parents most often discussed health concerns associated with maternal PKU syndrome (94 %) and least frequently discussed unplanned pregnancies (58 %). The most frequently used resource was a metabolic doctor (73 %); however, parents included mothers with PAH deficiency among the most helpful resources. Themes from open-ended responses and interviews emphasized qualities of parents' discussion with their daughters. Parents commented on the timing and how they presented the information to their daughters. They described challenges such as the emotional impact of the conversation as well as their daughter's decision-making and consequences of her actions. Lastly, they discussed advice for treatment compliance, resources, and ways to normalize the topic of maternal PKU syndrome. These results can help genetic counselors better understand the parent- daughter conversation so that healthcare professionals can better assess and inform families about maternal PKU syndrome.

Lessons Learned from the Development of an Educational Curriculum for Potential and Confirmed Female Carriers of Hemophilia

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Background: Hemophilia is an X-linked, inherited bleeding disorder, characterized by the deficiency or absence of a clotting protein in plasma, leading to prolonged bleeding in affected individuals. Priority has historically been on treatment of affected individuals, with less emphasis on identification and education of female relatives who may be hemophilia carriers. Carriers can sustain complications from injuries and surgery and they and their newborns are at risk for serious bleeding without appropriate care around childbirth. Women with a family history of hemophilia may be unaware of their potential carrier status or may not understand the implications for themselves and their offspring. Carrier identification and education helps promote optimal health outcomes and allows women and their partners to make informed family planning and healthcare decisions. Methods: A curriculum was developed for female relatives of individuals with hemophilia to provide accurate information about hemophilia, its inheritance, current care, and potential health concerns for carriers and their children. Curriculum materials were developed to assist health care providers in conducting educational programs for potential carriers. Materials include flyers, forms, agendas, slides, and a facilitator guide. The materials can also be used separately to provide genetic education for carriers and potential carriers. Results: Two pilot programs were held, with a total of 24 participants. Evaluations contained positive feedback and 23 attendees rated the program as "very good". Complete pre-post test results are evaluable for 19 participants; three had perfect scores on pre and post-tests, 12 improved their scores, and 4 had a drop in post test scores. The test and materials are under review to determine needed changes. Conclusions: Women were very satisfied with the program and learning took place overall. Final revisions will be made. The curriculum will be distributed nationally as a resource for education of female relatives of individuals with hemophilia.

An Assessment of College Students' Knowledge of the Importance and Awareness of Family Health History

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Background: In 2013, the Center for Disease Control (CDC) reported that 96 % of Americans believed family history was important to health. However, only about 30 % of Americans have tried to collect and organize their family history information. Purpose: This study assessed the importance of knowing family health history (FHH) amongst a college student population in the United States (U.S.). This study also explored factors that influence how FHH is disseminated and collected among the families of the students. Methods: 57 college students from Howard University in Washington, D.C. completed a 30 item survey; quantitative data was analyzed using a Fisher exact test. Results: Natural science students were more likely to know the components for an appropriate FHH. Students who agreed that knowing FHH could be beneficial in the prevention of cancer understood the importance of FHH, but there were no differences in the age and year of classification, and if the student had a genetic condition in regards to understanding the importance of FHH. Of the 41 participants that scored highly on the FHH importance scale, eight were not familiar with the genetic counseling profession. The majority selected their mothers as the relative most knowledgeable of FHH and felt that FHH should be discussed between ages 13 and 19. Popular barriers in collecting FHH included having a large family, differences in understanding medical information amongst relatives, and no one being diagnosed with a hereditary condition. Of those, a larger percentage of international students (versus U.S. born) selected spiritual beliefs, shame of having a condition, and guilt of passing the condition down to offspring as barriers. Conclusions: Students viewed FHH as important but noted significant barriers to collecting this information. As public educators regarding genetics, genetic counselors can play a critical role in reducing these barriers.

A Content Analysis and Readability Assessment of Websites for Lynch Syndrome

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Finding clearly written, accessible, high quality genetic information for a lay audience is challenging. Commercial testing sites may not be objective, health professional sites are complex, and blogs and Wikipedia are not authoritative. However, the U.S. government provides genetic information via the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC). President Obama signed the Plain Language Act to improve clarity in government communication. Moreover, about 36 % of U.S. citizens have "basic" or "below basic" health literacy – they can use simple texts with minimal medical or scientific jargon. Thus, this study sought to study the readability and quality of information for Lynch syndrome provided by the NIH and CDC on four websites: the Genetics Home Reference (GHR), Genetics and Rare Disease Information Center (GARD), the National Cancer Institute (NCI), and the Centers for Disease Control and Prevention (CDC). All sites were assessed on March 3–4, 2015 and judged readability with the Flesch-Kincaid Reading Ease (FKRE), which estimates text complexity on a 0–100 scale, and the SMOG, which estimates the years of education needed to understand a text and is widely used to assess health texts. Scores of 60–70 and 8.0, respectively, are considered generally accessible. Website quality was assessed using the DISCERN-Genetics tool. Scores of 60–80 % are of adequate quality. Content was not written at or below the 8th grade level for any site. The sites rated as follows: GARD (FKRE: 45.1, SMOG: 12.7), GHR (FKRE: 44; SMOG: 14), CDC (FKRE: 22.5, SMOG: 17.4), and the NCI (FKRE: 18.9, SMOG: 18.5). Website quality was rarely >60 %. The sites rated as follows: NCI (61 %), GARD (56 %), GHR (53 %), and the CDC (45 %). Although no site had optimal measures, GARD is the most accessible and is of similar quality to the NCI. Genetic counselors should be mindful of literacy

burden, proofread resources when possible, and potentially adapt and draft material from these sites using plain language as described in the free NIH Plain Language modules.

Development of a Knowledge-Based Survey Tool to Assess Comprehension of Genetic Counseling for Advanced Maternal Age

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Introduction: As of 2005, nearly 1 in 7 pregnant women in the U.S. satisfied criteria for advanced maternal age (AMA). Despite the need for genetic counseling services for this population, there is currently no method to assess comprehension of counseling on AMA. We created and validated a survey tool to assess comprehension of genetic counseling for AMA. Survey Development: The 2011 American Board of Genetic Counseling Practice Analysis was reviewed and used to generate a bank of knowledge-based questions regarding genetic risks of AMA by seven certified prenatal genetic counselors. The questions were consolidated based on content similarity and distributed to local (Indiana Network of Genetic Counselors) and national (NSGC) prenatal genetic counselors for review. These content experts were asked to rate each question on a scale of "essential", "useful, but not essential", and "not necessary" in the context of genetic information they wish to convey in a counseling session for AMA. A total of 74 responses were used to calculate a content validity ratio (CVR) for validation of individual survey items. The CVR was then compared to levels required for statistical significance for a two-tailed test with p=0.05. Of 19 items reviewed by prenatal genetic counseling content experts, 14 met significance and were included in the survey. Survey items underwent final expert review by a maternal-fetal medicine specialist and two prenatal genetic counselors for relevance to counseling goals and construction including format, verbiage, and response choices. Future Implications: We have developed and validated a knowledge-based assessment tool for genetic counseling for AMA in clinical settings. We plan to utilize this tool to characterize the results of genetic counseling for AMA and identify individuals who may need additional resources. Another goal is to compare comprehension of counseling in individual vs. group settings that may be used in low-resource environments.

An Effective Lesbian, Gay, Bisexual, and Transgender Cultural Competency Curriculum for Genetic Counseling Students

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The purpose of this study was to develop, implement and assess a replicable lesbian, gay, bisexual, and transgender (LGBT) cultural competency curriculum for genetic counseling programs. As research focuses on health care disparities and the unique needs of the LGBT population, professional training programs should respond with appropriate education to address these needs. The goal of our curriculum was to provide students with skills and attitudes to create an environment that promotes patient disclosure of sexual orientation and gender identity and knowledge to respond sensitively to this information. Learning objectives were created within four main themes: attention to relationship and family structure, inclusive and respectful communication, self-awareness and professional development. The themes were based on issues described in the literature, and published guidelines and competencies in fields similar to genetic counseling. Nine discreet curricular modules were created, which can be integrated into existing curricula or taught independently. Twenty-one second year genetic counseling students in the Joan H. Marks Graduate Program in Human Genetics at Sarah Lawrence College participated in the curriculum in the format of two workshops 1 week apart. Pre and post workshop measurements included the Sexual Orientation Counselor Competency Scale (SOCCS) and a knowledge survey. Comparison of pre and post-workshop scores revealed a significant increase in total SOCCS (t (20) = 5.78, p<.001), and skills (t (20) = 7.42, p < .01) and knowledge subscales (t (20) = 5.09, p<.001). There was no significant change in attitudinal subscale (t (20) = 0.48, p=ns). The knowledge scores significantly increased from 78 % (SD= 0.13) before training to 87 % (SD = 0.08) after training (t (20) = 3.48, p<.01). Student evaluations indicate overall satisfaction with content and presentation. This study indicates that the implementation of a LGBT curriculum improves genetic counseling students' LGBT cultural competency.

Genetics Literacy of Sickle Cell Disease: Assessing the Inheritance Knowledge of Young Adults Affected with Sickle Cell Disease

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Sickle cell disease (SCD) is an autosomal recessive hemoglobinopathy that affects an estimated 90,000-100,000 Americans. An additional 3 million Americans are carriers of sickle cell trait (SCT). Although SCD and SCT are relatively common in the United States, the literature reveals a lack of understanding of disease inheritance. Past studies have examined the knowledge of unaffected and affected adults, parents of sickle cell carriers, and unaffected college/graduate students. However, little is known about the genetics literacy of young adults affected with SCD. Young adults with SCD are a vulnerable population as they transition from pediatric to adult healthcare, and during this period of change and maturation, they are also of childbearing age. We administered a quiz-based questionnaire to assess the genetics knowledge of young adults affected with SCD at Boston Medical Center in Boston, MA. The questionnaire included fundamental SCD/SCT etiology and genetics questions in addition to higher-level SCD inheritance questions. Of 20 participants with SCD surveyed, the average percent of correct responses across all items was 70 %. Further analysis revealed a discrepancy in scores between the basic and advanced knowledge questions, with participants faring significantly better with the basic questions compared to the advanced. The results of this investigation suggest that even if affected young adults have a basic knowledge of disease inheritance, they may be unable to translate that knowledge into an advanced understanding of reproductive risk. This disconnect calls for further investigation into how to best educate the SCD population about inheritance and reproductive implications.

Shadowing of Clinical Genetic Counselors as an Admissions Criteria for Genetic Counseling Programs

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Exposure to genetic counseling is a strongly recommended prerequisite for entrance into genetic counseling programs. Shadowing a clinical genetic counselor is the most common method of fulfilling that requirement. Despite this, a survey of the literature revealed no studies documenting the benefits of this experience to either genetic counseling training programs or their trainees. This study queried both program directors and genetic counseling students to determine the perceived value of

shadowing and barriers to access, as well as identifying acceptable alternatives to shadowing. An online survey was distributed to 34 genetic counseling program directors and ~700 current genetic counseling students, response rates were 59 % and 33 % respectively. The majority of students (91 %, *n*=208) reported shadowing a genetic counselor prior to acceptance, though many (19 %, *n*=37) indicated that it was either "near to impossible" or "very difficult" to get this experience. Most described their experiences positively, with 94 %, of students (*n*=187) reporting that shadowing "confirmed their desire to pursue a career in genetic counseling." A substantial minority (47 %, *n*=94) had alternate experiences they considered "as beneficial as shadowing." Most training programs (80 %, *n*=16) reported shadowing as a recommended, but not required, admissions criterion. All program directors (100 %, *n*=20) felt that shadowing gives applicants a better understanding of the profession. Despite the difficulty in getting this experience, 85 % of directors (*n*=17) did not feel that the recommendation limits the applicant pool. Most program directors (83 % *n*=15) considered interviewing a genetic counselor an acceptable alternative; a minority (25 %, *n*=5) looked unfavorably on shadowing done exclusively in a non-clinical setting. Students and program directors both perceive value in shadowing a clinical genetic counselor. Given the level of difficulty in gaining this exposure, alternative experiences are also perceived to be of value to both populations.

LGBT Genetic Counseling: What do Cancer Genetic Counselors Want to Know?

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Roughly 3.5 % of the U.S. population identifiy as lesbian, gay, bisexual, or transgendered (LGBT), and increasing efforts have been made to educate healthcare providers on working effectively with the LGBT population. However, there is scant published literature specifically addressing the educational needs of genetic counselors in working with said population. This study aimed to identify the types of information genetic counselors desire regarding LGBT issues in the cancer setting. Ten cancer genetic counselors participated in semi-structured phone interviews. Interview questions addressed personal background affecting counseling of LGBT patients, genetic counselors' discomforts in counseling LGBT patients, perceived differences in counseling LGBT versus non-LGBT patients, interest in LGBT training, perceived gaps in LGBT training, and suggestions regarding LGBT training method. Inductive and cross-case analysis of interview data yielded 6 themes: genetic counselors' personal characteristics and experience influence their counseling with LGBT patients; genetic counselors do not experience discomfort with LGBT patients; background knowledge is important but cancer genetic counseling generally should not differ for LGBT patients versus other patients; LGBT training is needed; the biggest gap in LGBT training concerns education regarding the transgender population; LGBT training should take place in graduate school and through continuing education. Per interviewee recommendations such trainings should involve: personal experiences shared by LGBT individuals; information on medical and psychosocial issues specific to LGBT patients (especially transgender patients); and highlighting of unique issues related to different specialties. Future research should continue the investigation of desired LGBT education in different specialties within genetic counseling, explore transgender patients' experience in genetic counseling, and involve genetic counselors who self-identify as LGBT for insightful data regarding the unique needs of LGBT individuals in genetic counseling.

Genetic Counselors, Graduate Students and Upwards Evaluation of the Supervision Experience

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Clinical supervisors play a vital role in the training of genetic counseling students, yet they undergo no formal training in clinical supervision and work without established competencies. Genetic counselors hone their supervisory skills through a combination of trial and error, student feedback, consultation with colleagues, and the recollection of their own experiences with supervisors while in training (Lindh et al. 2003). While this may be adequate in many instances, it provides students with no safeguards of reliability, consistency or quality control in their clinical placements. The purpose of this study was to create a tool for the evaluation of clinical supervisors based on the competencies presented by Eubanks Higgins (2013). A preliminary version of this tool was designed to address each of the identified areas. A survey was created to refine this preliminary list, by assessing each in the light of three questions: 1. Is this competency easily measured? 2. Is this competency an important skill for supervisors to have? 3. Is students' feedback on this competency appropriate? Current students at the Joan H. Marks Graduate Program in Human Genetics and the genetic counselors and geneticists who supervise their clinical placements were invited to participate in an anonymous online survey administered using Survey Monkey. Over 95 % of students agreed or strongly agreed that the competencies can fairly assess a supervisor's abilities, and 92 % of supervisors felt that students could adequately evaluate them on each competency presented. On 22 out of 25 competencies, 90 % or more of students felt they could adequately evaluate their supervisors. One competency was removed from the evaluation tool and a new competency was created in response to students' comments. Most supervisors (over 80 %) described themselves as very or somewhat comfortable performing 24/25 competencies. Supervisors reported a high level of interest in further training. Assessment of clinical supervisors using the tool provided student feedback with strong internal consistency.

Strategies Used by Genetic Counselors to Mitigate the Effect of Low Patient Health Literacy

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Individuals with low health literacy are at risk for negative health outcomes and less informed decision making; however, it is difficult to identify such individuals. Health literacy mitigating strategies are recommended for use with all patients. Publications documenting which strategies genetic counselors routinely use and find helpful are lacking. In particular, the teach back technique has shown promise in the medical field, but has been described less in genetic counseling literature. The aims of this research study were to 1) determine which techniques genetic counselors use with patients versus what techniques they believe are helpful and 2) determine genetic counselors' knowledge and use of the teach back technique. We hypothesized differences exist between techniques used and techniques believed to be the most beneficial. We surveyed 365 genetic counselors using an online

survey with two matrices, each including the same 19 health literacy mitigating techniques. Participants were asked the frequency in which they use each technique with patients and how beneficial they feel each technique is for patients. Participants who volunteered were then contacted for interviews addressing knowledge of health literacy, teach back, and other techniques. All techniques involving the sharing of resources with patients showed some of the largest differences in belief of benefit versus reported utilization of the technique. Of the survey participants who believe the teach back technique is beneficial to patients, 77.4 % reported not using it very often. Interestingly, interviewees reported use of the teach back technique, but approximately half were not familiar with the label "teach back." The teach back technique is referred to by several names in general health care literature and is typically described without a specific label in genetic counseling literature. Genetic counselors do not appear to be using the teach back technique in proportion to their level of perceived benefit. This could be addressed via training concerning when and how to use the technique.

Genetics and Personalized Medicine: A Comparison of College Students' Perspectives

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Personalized medicine is an emerging practice in health care that promises improvements in disease treatment and prevention. The future of personalized medicine, however, depends on consumers and providers of medicine understanding its worth and becoming interested in it as a new form of health care. In 2010, the University of California, Berkeley (UCB) recognized this need and implemented the On the Same Page Project. The project gave incoming freshmen and transfer students the opportunity to have genetic testing, participate in personalized medicine-focused seminars, and take a survey related to their experience. This current follow-up study assessed the perspectives of those same students 4 years later and compared their perspectives to a control population of students at San Francisco State University (SFSU). The purpose of the study was to assess what impact exposure to genetic testing has on interest in and understanding of genetics and personalized medicine. A total of 701 UCB students (~13 %) and 381 SFSU (19 %) students participated in the survey. The student populations differed significantly in their knowledge of and interest in personalized medicine and genetic testing even after adjusting for covariates. The study found that after adjusting for covariates, UCB students scored higher on the genetics knowledge scale than SFSU students ($p<0.001$). However, after adjusting for covariates, SFSU students' reported awareness of genetic testing options and interest in genetic testing was higher than UCB students' reported level of awareness and interest ($p<0.001$). The results indicate that previous exposure to genetic testing could have an impact on genetics knowledge but does not necessarily increase awareness of or interest in genetic testing. This study contributes to the expanding literature on the public's knowledge of genetic testing by providing a better understanding of the factors that influence interest in genetic testing and the perspectives of educated young adults on the emerging field of personalized medicine.

Genetic Counseling Graduate Program Websites and Their Influence on Prospective Student Application Decisions

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Currently, 34 universities in the United States and Canada offer a minimum 2 year masters-degree in genetic counseling. The purpose of this study was to investigate what information was most useful to genetic counseling students when considering which programs to apply to and how program websites affected their application decisions. Current genetic counseling students and recent graduates completed an online survey, which asked what information on genetic counseling program websites was most influential in deciding to which programs to apply. Program/assistant/associate directors were also surveyed to solicit and compare their views to student responses. Chi square analysis and t-tests were used to determine significance of results, and a two-sample t-test was used to compare which factors students identified as important on a 5-point Likert scale compared to those identified by directors. Content analysis identified themes from students' open-ended responses about program website improvement. While directors noted limitations to making changes to their program websites, they were interested in how prospective students use their program website and what information they found most useful. Students indicated there were specific programs they chose not to apply to due to the difficulty of using that website. Students were significantly interested in all twelve program factors they were asked about, based on a 5-point Likert scale. A two-sample T-test showed that students and directors differed significantly in how important they thought information about academic requirements, application requirements, and course descriptions were in deciding which programs to apply to. Content analysis revealed three major themes of what students want from individual program websites: easy navigation, comprehensive information, and impression of the program. This information may help individual genetic counseling graduate programs to improve the functionality of program websites for prospective students and improve their applicant pool.

The Development of Visual Aids for Genetic Counseling About Multi-Gene Hereditary Breast Cancer Panels

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Cancer genetic counselors provide patients with customized information to assist in decision-making for genetic testing. Many counselors use visual aids during pre-test genetic counseling in order to improve patient understanding. A collaborative team developed visual aids tailored to the unique counseling aspects of multigene breast cancer panel testing including: review of relevant genes, associated cancer risks, genetic testing criteria, potential test results and result implications. A survey was designed to gather feedback on a subset of 10 visual aids, genetic counselor attitudes about perceived clinical utility, and current use of visual aids and multigene cancer panels. The survey was distributed to 540 cancer genetic counselors through the NSGC Cancer Special Interest Group's electronic listserv and 23 % responded (N=123). Participants were asked to provide feedback suggesting ways to make the ten images easier to understand. Responses were analyzed thematically utilizing QSR NVivo 10 software. Noted themes included: adjustment of labels used in figures, need for additional text clarifying components of images, vocabulary choice and operational definitions of terms used, visual representation including color choice and graphic selection, and the need to create more visual representations of information. The proposed visual aids were modified based on these themes and specific survey responses, and distributed for clinical use by cancer genetic counselors. As new tests are developed in the future, genetic counseling sessions and the visual aids utilized in them must evolve to incorporate these changes. By understanding the suggestions provided by cancer genetic counselors, future development groups can critically edit their images and maximize their potential clinical use. Future research should evaluate these visual aids to determine their impact on patient understanding in the pre-test genetic counseling session.

Investigation of the Common MELAS Mutation in the Northwestern Pennsylvania Amish Community: Mutation Frequency and Effectiveness of an Educational Intervention

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Mitochondrial (mt) disease affects an estimated 1 in 5,000 individuals. Prior to diagnosis of our index patient, mtDNA mutations were not reported in Amish communities. The index patient, from a Northwestern Pennsylvania Amish community, was diagnosed with MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, Stroke-like Episodes) and carries the common MELAS mutation, m.3243A>G in *MT-TL1*. Subsequently, two Amish families with different mitochondrial mutations were identified. This prompted a study to assess the efficacy of an educational intervention to increase understanding of MELAS and mitochondrial disease using pre- and post-intervention questionnaires, provide testing to an at-risk Amish community, and provide genetic counseling at the time of results disclosure. During a study visit to the community, an investigator-designed educational intervention was presented along with administration of questionnaires to assess knowledge. Samples were collected from 13 adults and two children and were analyzed using high-resolution melt profiling of the MELAS mutation. Genetic testing revealed m.3243A>G in 13 participants, with tissue-specific variations in heteroplasmy levels. Data analysis of questionnaires demonstrated limited increased understanding of educational intervention material. At a return visit, test results and their implications were disclosed and genetic counseling provided. Anecdotal experiences at that time support increased understanding and retention of educational intervention material. These findings suggest maternally-inherited mitochondrial disease may be under-recognized given the lack of previous diagnosis in these 13 participants. The public health significance is the potential for similarly unrecognized mitochondrial disease in the larger Amish community and in the general population due to the challenges related to diagnosis. Results of efficacy analysis of an educational intervention in this community can inform the development of educational interventions for the general population and health care providers about mitochondrial disease.

A Molecular Laboratory Rotation for Genetic Counseling Students: No Lab Required

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Identification, assessment, facilitation, and integration of genetic testing options constitute a practice-based competency according to the Accreditation Council for Genetic Counseling. Applicability of molecular genetics to medical genetics is also named as a curriculum content area. To address this need, the Johns Hopkins DNA Diagnostic Laboratory developed a molecular mini-course: an intensive, in-classroom, case-based exposure to pre-test, test, and post-test issues concerning clinical molecular diagnostic testing for inherited disorders. Goals of the course included gaining an appreciation of the issues faced in choosing, offering and explaining molecular tests; thinking about molecular labs and tests in new ways; forming a mental picture of how molecular testing happens and the framework of non-molecular support surrounding the technology; and gaining experience applying new knowledge and perspectives by working through clinical case examples. Over 7 cycles, 53 students took the course: 40 genetic counseling students, 6 clinical genetics residents, and 7 other students/observers. Using a survey of 8 Likert scale questions, we assessed whether course objectives were met and student satisfaction with content, detail, format, and facility. The structure for the first three cycles of the course was lecture with interspersed case exercises. In response to student critiques regarding increased interaction and an emphasis of cases over lectures, the course was restructured to be completely case-based. This led to significant increases in student approval of course format ($p<.05$) and detail of content ($p<.01$), and an increased ability to gain appreciation of issues involved in molecular testing ($p<.05$). Overall student satisfaction across all cycles was high (3.68+/− 0.47 out of 4.00, $n=47$). In conclusion, an in-classroom, case-centric course successfully provides an engaging student experience introducing the application of molecular science to clinical practice without the need for an in-lab placement.

The Interface Between Genetic Counselors and Obstetricians: Education Concerning Noninvasive Prenatal Screening

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Education has been suggested as a strategy to increase non-genetics professionals' knowledge of genetic testing and reduce potential harms. Research has indicated that genetic counselors may be an appropriate source of this education, but limited research has investigated their educational efforts. Purpose: This exploratory study aimed to examine how genetic counselors employed by laboratories clinically offering noninvasive prenatal screening (NIPS) educate obstetricians about this testing, what tools obstetricians utilize to increase their knowledge, how well educated obstetricians feel, and if obstetricians feel any aspect of their knowledge is deficient. Methods: An anonymous survey was distributed to NSGC members employed by laboratories offering NIPS. A second anonymous survey was distributed to obstetrician members of North Carolina Obstetrical and Gynecological specialty society. Open-ended responses were coded for themes. Quantitative data was analyzed using Fisher's-exact, Mann–Whitney U, and Kruskal-Wallis analyses. Results: Eighteen respondents completed the genetic counselor survey. The majority of genetic counselor respondents indicated they utilized one-on-one support and presentations to educate obstetricians, and the most frequently conveyed information included the nature of NIPS and implementing testing. Most participants indicated these educational efforts meet obstetricians' needs but additional education is needed with a focus on the limitations and non-diagnostic nature of NIPS. Nineteen obstetricians participated in the study. Obstetricians most commonly used maternal fetal medicine specialists and genetic counselors to increase their knowledge. The majority of participants indicated they felt moderately to completely knowledgeable concerning NIPS and needed additional information to provide adequate counseling. Discussion: Obstetrician participants' knowledge of NIPS may be increasing, but additional education is needed to address obstetricians' needs and ensure published guidelines are followed.

LEND-Genetics Fellows: Long-Term Assessment of Interdisciplinary Skills, Service and Leadership

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2. Children's Hospital at Montefiore

The purpose of this study was to assess the long-term outcomes of the Leadership Education in Neurodevelopmental and Related Disabilities Genetics (LEND-Genetics) program and the interprofessional (IP) skills and attitudes of LEND-Genetics fellows. This is the first research involving interprofessional education (IPE) for genetic counseling (GC)

students and the first assessment of the LEND-Genetics program. LEND-Genetics programs provide formal IPE to associated GC programs. First, we performed a retrospective assessment of genetics fellows nationally using 210 archived follow-up surveys. Second, IP skills and attitudes of former genetics fellows of the Rose F. Kennedy University Center for Excellence in Developmental Disabilities in Bronx, NY were assessed using the Team Skills Scale (TSS) and Attitude Toward Health Care Teams (ATHCT) scale. The majority of fellows nationally work with maternal child health, underserved and vulnerable populations. Most (74 %) work in hospitals, are more likely to work for government agencies and less likely to work in the private sector compared to data in NSGC's Professional Status Survey. Over 85 % report leadership activities, mainly in clinical or academic settings. The response rates to the TSS/ATHCT surveys were 40 % (8/20). The mean TSS score was 79.8 % (categorized as high) and positively associated with time. The mean ATHCT total, team efficiency and team value subscale scores were 83.2 %, 78.3 % and 84.5 % (all high). Fellows' team skills and attitudes toward team productivity were higher than scores reported in IPE research on other disciplines. Fellows' belief in teamwork positively effecting patient care was only stronger than some health care professionals. Our assessment shows that, nationally, the LEND-Genetics program is achieving its aims, and fellows' team skills and attitudes from one program rank highly amongst other health disciplines. IP skills are a core competency for genetic counselors. The LEND-Genetics program can serve as an IPE model for genetic counselor training.

Sex Education and Intellectual Disability: Perspectives and Insights from Pediatric Genetic Counselors

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3. University of Kentucky

Intellectual disability with or without other anomalies is a common referral for genetic counseling. Sessions may include discussions of reproductive implications and other issues related to sex education. Patients with intellectual disability (ID) regularly meet barriers when trying to obtain sex education due to the beliefs and practices of unaffected individuals such as caregivers, family members, and health care professionals. We surveyed genetic counselors to explore the frequency with which they are asked to provide sex education counseling and their comfort in doing so for patients with ID ages 9–17. Caregivers and patients most frequently asked about puberty, sex abuse prevention, and reproductive health. Genetic counselors were most comfortable when they could provide sex education counseling within the context of a particular condition or constellation of features. They were least comfortable when there was a lack of familiarity with the patient, caregiver, or the family's culture. The most frequently cited barriers that prevented genetic counselors from providing sex education counseling were lack of time, lack of training, the patient's ID being too profound, and the thought that genetic counselors should not be responsible for providing sex education counseling. While many respondents recognized that providing sex education counseling is not considered within the scope of a genetic counselor's practice, respondents also acknowledged that they should be prepared for such discussions and were interested in having access to specific online and print resource guides specifically designed for use by genetic counselors to provide to patients with ID and their caregivers. Genetic counselors as well as medical professionals of all disciplines are encouraged to embrace the role of advocate and broach the issue of sexual health with caregivers and patients by directing them toward educational resources, if not providing sex education themselves to effectively serve the needs of patients and caregivers.

Evaluation of the Impact Program, a Disability Immersion Experience, in Genetic Counseling Education

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The purpose of this study was to evaluate a disability immersion experience for genetic counseling students in the Joan H. Marks Graduate Program in Human Genetics at Sarah Lawrence College. The Impact Program offers an opportunity for students to spend a day with a family who has a member with Down syndrome (DS). Genetic counseling programs have few models to guide training on disabilities despite a practice based competency that entry-level genetic counselors must understand the lived experiences of people with genetic conditions. This study is an outcomes assessment of one model. Students who participated in the Impact Program from 2012 to 2014 were surveyed to assess the program's effectiveness in enhancing their confidence and skills serving the disability community. The response rate was 49 % (42/86) with the majority of respondents being female (95 %) and under the age of 30 (98 %). Of those currently practicing as genetic counselors, 73 % worked in a prenatal setting and 45 % in pediatrics. Likert 5 point agree/disagree questions about whether the program 1) enhanced awareness of psychosocial issues, comfort level and knowledge of disability scored an average of 4.1 (agree), 2) enhanced skills counseling prenatal patients with a diagnosis of DS scored 3.28 (neutral/agree) and, 3) enhanced skills counseling those with a postnatal diagnosis scored 3.5 (neutral/agree). 73 % of participants commented that seeing positive interactions among family members and the member with DS was the most memorable part of their experience. Suggestions for improving the program include clarification about expectations, expanding diversity beyond DS and fostering long-term relationships with families. This study demonstrates that the Impact Program helps students expand their understanding about, and confidence with, the lived experiences of individuals with DS. Disability immersions programs are important in the training of genetic counselors in order to facilitate the provision of quality services to individuals with disabilities.

Medicine's Future: An Education Program Designed to Improve Genomics Practice in a Community Hospital

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1. The Jackson Laboratory
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3. Dowling Associates

Education of practicing health professionals is likely to be one factor that will speed appropriate integration of genomics into routine clinical practice. Yet many health professionals, including physicians, find it difficult to keep up with the rapid pace of clinical genomic advances and are often uncomfortable using genomic information in practice. Methods: Having identified the genomics educational needs of physicians in a Silicon Valley-area community hospital, we developed, implemented, and evaluated an educational course, entitled Medicine's Future: Genomics for Practicing Doctors. The course structure and approach were based on best practices in adult learning, including interactivity, case-based learning, skill-focused objectives, and sequential monthly modules. The course content included fundamental skills in risk assessment, assessing utility and validity of genetic testing, interpreting genetic test results, and incorporating genetic information into management applied to a variety of disease areas – complex disease, prenatal medicine and pediatrics, cancer, cardiology, neurology. Results: Physicians participating in the 10-module course demonstrated significant gains in knowledge of risk assessment (approximately 37 % increase); ordering, interpreting, and using results of genetic tests (approximately 65 % increase); and providing education and

guidance to patients (more than 100 % increase). Confidence in skills related to genetic testing, referral decisions, and patient communication also significantly improved. Six months following the course, the majority of participants reported that they had changed their practice to incorporate skills learned during the course. We observed a correlation in increased genetic counseling referrals in the months the course was held. Conclusion: We believe the adult learning principles underlying the development and delivery of Medicine's Future were responsible for participants' outcomes.

Development of an Interactive Online Clinical Whole Genome Sequencing Educational and Engagement Tool

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The promise of clinical whole genome sequencing (cWGS) is overshadowed by the vast amounts of complex data, difficulty in translating data into actionable information, and the need to communicate information in lay language. Existing websites allow genomic exploration but are neither consumer friendly nor routinely include educational or interactive components. We developed a free, web-based "community" where individuals who have undergone cWGS can explore their genome using the MyGenome application and Understand Your Genome® Community. Those who have not had cWGS can join and explore a demonstration genome. The goal is to create an interactive, engaging workspace to increase individual genomic literacy and expand the personal utility of cWGS data. Individuals learn about medical conditions, including clinically significant variants and pharmacogenetic indications identified through their screening and can link to educational web resources. Individuals can access variant information (allele frequency, gene callability, inheritance patterns, amino acid changes). As individuals learn of variants through academic or lay literature, they can use the chromosome browser feature to navigate to these areas within their genome. Participant feedback has been positive. Website statistics demonstrate frequent and return visits. Participants overwhelmingly request the ability to follow genomic discoveries, research their variants, share genomic information with family, friends and health care providers, and donate their genome to research. Participants are also interested in networking and identifying individuals within the community with similar genomic findings. The development of an online educational community has been positively received by individuals engaged in cWGS. As we continue to explore the utilization of genomic information and struggle with the definition of "value", understanding the motivations for sharing genomic information and the opinions on the key components and features of the application will be important in building an actively engaged community.

Bringing Sociometrics to the Classroom

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Literature suggests that genetic counselors should keep their feelings from influencing a session. This expectation is introduced early in training, but we historically haven't taken the extra step to help students identify and reflect on personal biases. Here we introduce a structured method to encourage students to ponder complex issues, at both the beginning and end of their first year. Over the past 3 years, the Joan H. Marks Graduate Program in Human Genetics has used sociometry as a tool to evaluate values and beliefs. Sociometry, a quantitative method for measuring social relationships, is defined as "the inquiry into the evolution and organization of groups and the position of individuals within them." We take precautions to create a safe space for students to be honest without having to disclose their beliefs to classmates or us. Students and instructors anonymously answer all 12 questions. Questions range from ethical issues to personal choices to professional situations. Responses for each question are tallied and displayed. Results indicate: (a) there has been only one unanimous response; (b) the percentage of individuals who believe termination for a given reason is ethical always exceeds the percentage of individuals who would personally terminate for this indication, (c) the trend from Fall to Spring stayed consistent across all years for 1/3 of questions, and (d) Each year, one particular question, about potential cultural practices, significantly changes between semesters, but in differing directions. 2014–2015 was the first year students tracked and compared their Fall and Spring results. Each student had one to five discrepant answers between Fall 2014 and Spring 2015. To respect confidentiality we are not able to assess these individual changes further. In our experience this exercise not only forces individuals to be mindful of their own value system; it also demonstrates that even in a small, "homogeneous" field, there is a wide range of beliefs. This exercise generates insightful discussion and is a valuable tool to incorporate early in training.

Parental Perspectives of Array Comparative Genomic Hybridization Educational Tool

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Array comparative genomic hybridization (arrayCGH) is the standard genetic screening test for common pediatric referrals such as unexplained developmental delay or multiple congenital anomalies. However, healthcare providers often hesitate to address all possible array results with parents before testing children due to the complex or sensitive nature of some potential results. In an effort to better educate parents, an informational pamphlet describing arrayCGH and the possible results was created and distributed to parents of children who had arrayCGH testing after the test was ordered. A survey was developed to capture parental opinions of arrayCGH and the pamphlet; in addition, after reviewing the pamphlet, their knowledge level of arrayCGH was evaluated with a ten-topic quiz located at the end of the survey. Results demonstrate parental desire for pre-test knowledge of all potential results, particularly variants of unknown significance, incidental findings, and areas of homozygosity. Importantly, only 14–21 % of parents recalled discussing these particular result types with their providers prior to testing. Despite this lack of pretest counseling, the quiz questions about these respective result types were answered correctly by 80–100 % of parents. Overall, the pamphlet appeared to increase parental understanding of arrayCGH, improve their comfort level with testing, and better prepare them for the different potential result types.

Measuring the Effectiveness of a Genetic Counseling Supervision Training Conference

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Genetic Counselors (GC) who receive formal training report increased confidence and competence in their supervisory roles. The effectiveness of specific formal supervision training has not been assessed previously. A day-long GC supervision conference was designed based on published supervision competencies. Participants completed online pre, 1-week post, and 6-months post-conference surveys with questions regarding supervision experience, perceived supervisor competence and confidence

as measured by Psychotherapy Supervisor Development Scale (PSDS), and self-reported agreement in ability to perform 6 supervision competencies. Paired t-test was used to compare PSDS scores between pre and post conference. McNemar's Chi-squared test was used to determine if the conference meeting had an effect on GC supervision competencies. 36 participants completed the pre-conference survey, 32 the 1-week post-conference survey, and 19 the 6-month post-conference survey. PSDS scores were significantly increased 1 week ($p<0.001$) and 6 months ($p<0.001$) following the conference. For three supervision competencies, attendees were more likely to agree they were able to perform them after the conference than before. These competencies included: "provide a balance of challenge and support appropriate to student developmental level and experience" ($p=0.013$), "use supervisory methods appropriate to students' level of conceptual development, training, and experience" ($p=0.003$), and "deal with student resistance in productive ways" ($p<0.001$). These effects remained significant 6 months later. For the three remaining competencies, the majority of supervisors agreed they could perform these before the conference; therefore, no change was found. This conference increased the perceived confidence and competence of the supervisors who attended and increased their self-reported ability to perform certain supervision competencies. We recommend additional supervision training be provided to supervisors based on the GC supervision competencies with which supervisors are least comfortable.

VII. ELSI

Potential Clinical Use of *APOE* Testing in the Population at Risk for Traumatic Brain Injury: A Survey of National Collegiate Athletic Association Student-Athletes

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Routine use of *APOE* genotyping, with its association to increased risk of late-onset Alzheimer's disease (LOAD), is controversial and has been discouraged by professional organizations, in part because predictive information on LOAD is not clinically useful. Recent studies indicate that *APOE* genotype is also associated with the risk of a poor recovery from traumatic brain injury (TBI) suggesting that *APOE* genotyping may have clinical value for athletes, either in determining the level of risk associated with participation in high TBI incidence sports, or in personalizing treatment of TBI and making decisions around return-to-play. This study examined the interest of National Collegiate Athletic Association (NCAA) student-athletes in *APOE* genotyping, the barriers to testing, and their perception of the potential ramifications of APOE genotyping. A survey of 843 Division I, II and III NCAA athletes indicated widespread interest in *APOE* genotyping. The vast majority (92.5 %, $n=780$) were willing to test if it was required by the school, however most indicated that they would test if it were voluntary (75.9 %, $n=639$). Student-athletes seemed largely unconcerned with potential ramifications of testing, and indicated that they would tell their coaches (75.7 %, $n=638$), their parents (86.1 %, $n=725$) and their doctors (86.0 %, $n=725$). Students suggested that they did not expect testing to impact their behavior (59.4 %, $n=500$) or their style of play (67.4 %, $n=568$). Students were interested in learning more about their risk for LOAD and few indicated this made them less likely to test (12.4 %, $n=104$). Despite this apparent lack of concern, most students indicated that they would prefer having the option of genetic counseling (51.5 %, $n=434$) and the majority expressed an interest in meeting with a genetic counselor to discuss their results (62.5 %, $n=527$). Study findings suggest a need to consider the appropriate use of *APOE* genotyping in this setting, and the role that genetic counselors might play in ensuring that athletes are adequately informed of all potential harms and benefits.

Development of Recommendations for Ordering Clinicians with Minimal Genetics Background from the ClinGen Consortium Cconsent and Disclosure Recommendations Committee

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2. University of Louisville
3. University of Colorado School of Medicine
4. Sarah Lawrence College
5. Stanford University
6. Hospital for Sick Kids Genome Diagnostics Laboratory
7. Johns Hopkins University
8. RTI International
9. University of North Carolina
10. Natera, Inc.
11. Northwestern University Feinberg School of Medicine
12. University of Michigan, Division of Molecular Medicine
13. Mayo Clinic, Division of Laboratory Genetics

Introduction: Molecular genetic testing is increasingly ordered by medical providers in a variety of specialties. Guidelines and recommendations to strike a balance between ensuring high quality pre- and post-test counseling and unnecessarily restricting access are lacking for ordering clinicians who lack expertise in genetics. We recruited stakeholders representing viewpoints of genetic counselors, MD geneticists, ethicists, pediatricians, policy experts, and patient advocates to join the Consent and Disclosure of Results (CADRe) committee, a working group of the National Institutes of Health's ClinGen consortium, to explore possible solutions to this quandary. Purpose: Summarize ethical, legal, social, medical, logistical issues (ELSIPlus) stakeholders deemed critical in ensuring high-quality genetic counseling when non-genetics providers order molecular tests. Methods: We will present results from the completed phase 1 of our project, during which we convened three conference calls between October and December, 2014. Discussion was minimally guided by the study's Primary Investigators to generate initial topics for consideration. Calls were transcribed and analyzed for themes using framework analysis. Results: Participants (n = 14) enumerated many topics to consider, including: test and disease characteristics, provider/patient misinterpretation, growing cultural awareness of genetic testing in the general public, patient preferences, varying quality and availability of educational materials, necessity for a follow-up plan, cascade testing, context of testing, emotional burden, lab and clinician reporting methods. Conclusion: Thus far, the CADRe committee has developed a list of ELSIPlus topics to consider in pre-and post-test counseling when ordering genetic testing, and are pursuing development of recommendations suitable to incorporate into ClinGen guidelines for actionability and as an aid to clinical practice for non-geneticists.

A Qualitative Study of Adolescents' Understanding of Biobanks and Their Attitudes Towards Participation, Re-Contact and Data Sharing

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Background: While biobanks are important resources for advancing personalized medicine, there are many ethical concerns about them including

consent, re-contact and data sharing. These concerns are more pronounced when children and adolescents are included. Despite biobanks' increasing prevalence, little is known about adolescents' familiarity with biobanks and their views of key governance issues. Methods: Qualitative methods were utilized due to the limited existing data. An investigator conducted semi-structured interviews with adolescents between 15 and 17 years old. All interviews were audiotaped and transcribed. Two investigators analyzed transcripts and resolved discrepancies through consensus. Results: We conducted 18 interviews before reaching data saturation. Four participants (22.2 %) had previously heard of a biobank. Many participants had misunderstandings about biobanks, some of which persisted after education. Participants believed that participating in a biobank would benefit others through scientific research. Many participants were unable to identify risks of participation and few were concerned about loss of privacy. Thirteen participants (72.2 %) were willing to enroll in a biobank, 1 (5.6 %) was not and 4 (22 %) wanted more time to consider enrollment. Participants believed that, if they were unable to provide assent when enrolled, they should be re-contacted at the age of majority and their data should not be shared until this time. Participants emphasized the importance of being aware of enrollment and the possibility of disagreeing with their parents. Conclusions: Participants' misunderstanding of biobanks suggests that assent may not be adequately informed without additional education. While the adolescents had positive attitudes towards biobanks, they emphasized the importance of awareness and involvement in the decision to participate. Nonhuman subjects approaches may risk the loss of trust when individuals become aware of their participation.

Directiveness in Genetic Counseling: Adapting to Increasingly Complex Tests

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A key ethos of genetic counseling is to be non-directive and to promote patient autonomy by illuminating all relevant choices and outcomes. The goal of this study was to discover the extent that patients prefer genetic counselors to be non-directive regarding genetic testing options. Patients and genetic counselors at four hospitals near Richmond, Virginia were recruited to complete a brief survey concerning their preferences regarding autonomy. Surveys measured patient decision-making preferences prior to their appointment and matched post appointment surveys, which measured how they felt decisions were made. Prenatal genetic counselors were asked to complete a similar questionnaire after the appointment asking about their perceptions of how decisions were made. A sample of 32 patients and 5 genetic counselors was collected. The majority of patients, 41.9 %, wanted decisions about genetic testing to be made on an equal basis with genetic counselors while 38.7 % wanted to make the decision with some input from the genetic counselor. When patients' expectations did not match the outcome, it was more commonly noted that patients preferred the genetic counselor to be directive or to make decisions on an equal basis with them, but felt the session was non-directive. This finding was noted in 20.7 % of participants. Surveys from genetic counselors were compared to those that patients completed after their appointment. Discordance was found between patient and genetic counselor perceptions of when a directive technique was used. All counselors surveyed reported the patient was the primary decision maker for genetic testing. 83.9 % of counselors felt they had no input on the decision while only 13.3 % of patients answered that they made the decision independently ($p<0.001$). The decision-making preferences of prenatal genetic counseling patients tend to vary. There is substantial discordance between stated decision-making roles of counselors and their patients. This discordance requires further investigation so genetic counselors can provide the best care for their patients.

Developing an Abbreviated Consent for Broad Data Sharing in the Clinical Setting

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Genomic data sharing between clinicians, clinical and research laboratories, and patients is essential for improvements in genomic medicine. The need for broad access to data must, however, be balanced with the need to respect patient autonomy and privacy, and consent should be obtained before sharing individual-level data. While obtaining consent for data sharing in the traditional research setting is clear, obtaining consent for data sharing in the clinical setting has been hindered by lack of time and resources at both ends of the clinical encounter (clinician and clinical laboratory). To address this need, the National Institutes of Health's (NIH) Clinical Genome Resource (ClinGen) has developed a one-page consent form for broad data sharing in the clinical setting, facilitating the deposition of de-identified genetic information into case-level repositories. This consent form is intentionally a single page in length to allow for quick initial review in the clinical setting, with supplemental online content detailing key topics, such as what constitutes de-identification and the risks and benefits of data sharing. The consent is consistent with the intent of the NIH Genomic Data Sharing Policy and includes all applicable components recommended by the National Human Genome Research Institute's Informed Consent Resource. Clinical laboratories and clinics will be encouraged to use this form as a guide to facilitate their data sharing efforts, and to incorporate the language as provided, or with appropriate modifications, into existing clinical consent forms for testing and treatment. Prior to public dissemination, ClinGen intends to review this form for acceptability and feasibility with focus groups of clinicians, clinical laboratories, and a newly created community engagement board, composed mostly of patients and patient advocacy representatives. ClinGen hopes this consent form will be widely disseminated and incorporated into the clinical care process – providing patients a straightforward way to share their genetic and health information for both research and clinical use.

Enriching the Clinical Ethics Education for Genetic Counseling Graduate Students Through Team-Based Learning

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We report on the use of team-based learning (TBL) to enrich the clinical ethics education for genetic counseling graduate students. TBL is a uniquely powerful form of small group learning that focuses on student preparation outside of class and application of knowledge in class, thus providing a flipped classroom experience. Genetic counseling training programs must address ethical issues in genetics to comply with accreditation standards published by the Accreditation Council for Genetic Counseling (ACGC). At the University of Texas Genetic Counseling Program (UT GCP), the ethics requirement has traditionally been met by a graduate school course that uses a lecture format followed by small group discussions. As the majority of students taking this course are PhD students, it is geared towards laboratory ethics, with topics such as, the humane care and use of animals in the laboratory. Historically, in course

evaluations, the UT GCP students have consistently commented on how a lot of the material in the course is inapplicable to the practice of genetic counseling, with comments such as, "it just isn't relevant!" In 2014, the graduate school moved to a core curriculum model and the UT GCP reformatted the ethics course to integrate more relevant clinical ethics training. Using a TBL approach with four 90 minute sessions, case examples, and the newly published text, Ethical Dilemmas in Genetics and Genetic Counseling by Janice Berliner, we discussed relevant ethical issues to the clinical practice of genetic counseling. At the conclusion of the course, the students had overwhelmingly positive responses for the new class format. They enjoyed and appreciated the TBL format, the cases examples and the ethics textbook. In conclusion, we are pleased with the outcome and will continue to explore additional opportunities, such as TBL, to enhance the ethical training of our students.

Counseling Close to Home: Genetic Counselors' Experiences Providing Genetic Counseling to Their Own Family Members

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Genetic counselors are trained to provide counseling and communicate personalized genetic information to clients and their families. When requests for counseling comes from the counselor's own family member outside the clinic, should that counselor still provide such services? Ninety-nine percent of physicians have been asked to provide medical advice to family members and the majority has provided medical advice. Similar studies exploring this issue among genetic counselors have not been reported. The purpose of this study was to examine perceptions and experiences of our genetic counseling colleagues, to encourage a discussion about this issue among the profession. In the present study, 423 genetic counselors and genetic counseling students completed a 70-item web-based survey exploring genetic counselors thoughts and experiences counseling family members. Qualitative data were thematically coded and statistical analyses of both qualitative and quantitative data was performed to look for significant trends. Seventy-three percent (n=301/410) of respondents have been asked to provide genetic counseling and 57 % (n=257/423) have actually provided counseling, personalized genetic information or risk assessment to family members to outside of a clinic setting. Only a small fraction of respondents (11 %; n=45/420) have received training or discussed this issue with mentors; those who reported they have were less likely to have provided genetic counseling to a family member (p= 0.0459). Respondents who have provided genetic counseling to family members were more likely to think their colleagues would also provide counseling while those who have not were more likely to think their colleagues would refer to an unrelated genetic counselor (p<0.0001). Based on the diverse opinions obtained and lack of consensus, we believe that further discussion of this topic may help guide how genetic counselors might respond to requests from family counseling outside of a clinical setting.

Patient Education and Informed Decision-Making: An Assessment of Consent Documents for Noninvasive Prenatal Genetic Screening

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Ethical concerns have highlighted the need to strengthen informed decision-making for noninvasive prenatal genetic screening (NIPGS). Widespread and unregulated uptake, aggressive commercial marketing, misrepresentation as a diagnostic test, low procedural risk, and routinization have all contributed to diminished rigor in the consent process for NIPGS. There is a pressing need for adequate patient education, given the rapidly transforming landscape of NIPGS and increasing patient preference for noninvasive procedures. In this study, we evaluated informed consent documents (IC) provided to patients. Here we (1) describe the content of currently existing IC; and (2) based on this assessment, offer recommendations for such documents. We collected written patient education and consent documents created by laboratories and clinics by searching online and soliciting from genetic counselors and other clinicians. IC (n=32) were assessed for readability, attention to elements of informed consent, and completeness of information about the test and the conditions potentially detected. About half of IC failed to include phenotypic descriptions of the conditions screened. 53 percent mentioned the possibility of false positives. 56 percent discussed post-test genetic counseling. Commercial IC (n=22) were longer and written at higher reading levels than non-commercial IC (n=10) and less often stated that NIPGS only screens for certain conditions. Based on our findings, we recommend that women be offered a consent form that is separate from the lab order form and offered a copy to take home. IC should be written at an appropriate reading level and include information on the benefits and risks of NIPGS and the conditions screened. Limitations and alternatives to NIPGS should be clearly stated, including the option to decline all prenatal screening. Finally, the rapid evolution of NIPGS means that IC likely need to be updated frequently and should always be accompanied by verbal counseling by a qualified health provider.

Exploring the Importance of Guardianship for Individuals Coming of Age with 22q11.2 Deletion Syndrome

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22q11.2 deletion syndrome (22q11DS) is the most commonly occurring microdeletion syndrome, and has wide phenotypic variability among affected individuals. In addition to medical manifestations symptoms often encompass an array of behavioral, psychological, and cognitive difficulties. Individuals with 22q11DS tend to have a unique cognitive profile, with specific deficits in executive functioning and social cognition that may impact reasoning and decision-making, as well as make them more vulnerable in social contexts. In addition to this, many studies have demonstrated a significantly increased risk for major psychiatric illness in individuals with 22q11DS. Guardianship is a legal process designed to protect the best interests of uniquely vulnerable individuals in adulthood. Accordingly, pursuing guardianship may be a worthwhile consideration for some parents of adolescents with 22q11DS. Nonetheless, there is an absence of such information routinely accessible to parents in the context of this specific clinical population. The goal of this project was to address this need by conducting a primary literature review on both 22q11DS and legal guardianship. Subsequently, a novel informational resource targeted for parents of adolescents with 22q11DS was developed in the form of a tri-fold brochure. The brochure was modified for readability and suggestions were sought from several parents of individuals with 22q11DS, family and disability attorneys, and a social worker. These suggestions were incorporated into a final revision of the brochure. The brochure provides an overview of guardianship and its potential relevance for individuals with 22q11DS, offers guidance for families considering this decision, and directs parents to further resources. Ultimately, tailored guardianships may be an appropriate source of protection for some families of adolescents with 22q11DS to consider. While the brochure

produced is targeted for our specific clinic population, our hope is that this resource can be modified to suit similar clinic populations in the future.

Views of Genetic Counselors on the Use of Preimplantation Genetic Diagnosis for Social Sex Selection Purposes

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Introduction: Preimplanatation genetic diagnosis (PGD), a technology that allows genetic testing of an embryo before implantation into the uterus, was first used to select for embryos at risk for X-linked diseases. Use and indications have expanded greatly in the past two decades. In some instances, prospective parents are using this technology to select for male or female children for purely social purposes. Purpose: This study aims to examine the views of genetic counselors on the use of PGD for social sex selection. Methods: A survey was conducted using the online website survey monkey's platform and sent to members of NSGC through an eblast. A total of 342 responses were received with a response rate of 11 %. Results: A majority of respondents (64 %, *n*=130) expressed concerns about the future use of PGD for social sex selection, but were highly supportive of a woman's right to choose regardless of their views on sex selection (63 %, *n*=129). Respondents expressed concerns that sex selection may create a male–female population imbalance in other countries (53 %, *n*=108), that sex selection reflects prejudice against women in other cultures (63 %, *n*=127), and that sex selection might lead to other, more offensive types of trait selection (70 %, *n*=142). Most believed that the use of reproductive technology to select traits is likely to become more commonplace over time (72 %, *n*=148).
Conclusion: Genetic counselors are conflicted as regards current practice in social sex selection. They express strong personal discomfort with sex selection for non-medical purposes, but believe in the right of the patient to terminate a pregnancy for any reason.

VIII. Genetic/Genomic Testing

Parental Reasons for Participation and Reactions Toward Return of *CYP2D6* Research Results

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CYP2D6 contributes to the metabolism of more than 25 % of drugs prescribed in a clinical setting and pharmacogenetic testing for *CYP2D6* can inform drug selection and dosing. Knowledge of parental reasons for participation in CYP2D6 pharmacogenetic testing and reactions to the return of results could inform decisions about returning incidental genomic results relevant to drug response. The goal of this study was to assess parental reasons for participating in research involving the return of their child's CYP2D6 research results and reactions to the receipt of results. Following the return of CYP2D6 pharmacogenetic research results, we conducted qualitative interviews with a subset of 61 parents enrolled in the eMERGE study at Cincinnati Children's Hospital Medical Center. All interviews were recorded and transcribed verbatim. Transcripts were coded and analyzed for major themes and subthemes. Thirty-one parents of children who were naïve to opioids and 30 parents of children with previous opioid exposure participated in the qualitative interviews. No topical differences were seen between the two groups. The majority of parents identified helping their child or learning about their child's health as a reason for participating. Some parents discussed more altruistic reasons. In the parents' reactions to results, two themes emerged. One theme was "perceived normality," which consisted of the subthemes that the "child is medically normal" and that the "child is socio-culturally normal." The second theme, "emotional appraisal filtered through expectations," consisted of a range of emotional reactions to the results (e.g. "result was interesting"; "result was surprising"; etc.). Overall our findings suggest that parents participate in pharmacogenetic research because they perceive benefits for the child or themselves. Our findings suggest that CYP2D6 research results will not affect parental interactions with children and that "genetic essentialism" is not a concern because parents do not regard their child differently.

Evaluating Changes in Patient Anxiety Regarding Classic Cancer Genetic Testing Versus Expanded Multiplex Cancer Genetic Testing: Pilot Study

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Introduction: Five to ten percent of breast cancer cases are caused by an inherited germline mutation. BRCA1/2 genes are associated with a hereditary predisposition to breast cancer. Other causative genes without clear screening guidelines are being analyzed. Healthcare providers now decide whether testing of the two single genes or multiplex testing is most appropriate for patients. Consideration of possible anxiety regarding poorly defined risks and absence of guidelines has not been studied. Methods: Individuals diagnosed with breast cancer undergoing genetic testing were invited to participate. Participants completed a baseline State-Trait Anxiety (STAI) questionnaire at their pre-test genetic counseling session, and completed the same STAI questionnaire and a Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire after the post-results discussion. Anxiety scores were analyzed using paired sample t-test, Kruskal-Wallis, and Mann–Whitney U-test. Results: Of twenty individuals who agreed to participate, nine completed all questionnaires. Results showed five with negative results, two with positive, and two with variants of uncertain signigificance (VUS). Participants with positive and VUS results showed non-significantly increased mean anxiety scores by STAI. Differences in anxiety between those with positive results and those with negative results trended toward significance. Two individuals with positive mutations in genes other than *BRCA1/2* showed higher post-results anxiety levels on the MICRA scale than did two participants with VUS results. Conclusion: We were unable to explore differences in anxiety between those who underwent classic *BRCA1/2* testing versus those who pursued multiplex cancer gene testing due to small cohort size. The gene in which a mutation or VUS was found appeared to affect overall changes in anxiety as differences approached significance even at small sample size. A larger population may elucidate what factors influence changes in anxiety between patients with negative, positive, or VUS test results including the gene in which a finding is made.

ACMG Incidental Findings: Genetic Counselors' Views on Disclosure

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The utilization of whole exome sequencing (WES) is increasing in the clinical setting. WES technology often generates incidental findings (IF), which are findings that are not relevant to a diagnostic indication for which the test was ordered. The American College of Medical Genetics and Genomics (ACMG) has identified mutations in 56 genes that they recommend searching for when labs conduct WES. This group of 56 genes, termed the minimum list, includes mutations associated with 24

medical conditions. This study investigated genetic counselors' views on disclosure of IF's on the minimum list. A survey was sent to 3,209 genetic counselors through an e-blast to the membership of the NSGC; 88 responses were received. Most participants (74 %, *n*=51) indicated an expectation that patient preferences would be established by the lab prior to testing. This finding implies that respondents believe the duty of informed consent should fall primarily on the lab rather than the clinician. This view is in direct contrast to the ACMG recommendations, which place the burden of obtaining informed consent on the clinician. In fact, labs are not capable of obtaining informed consent; they can only document what was obtained by the clinician. Once results are reported, 81 % of counselors (*n*=57) reported feeling an obligation to disclose any pathogenic mutations of genes on the ACMG's minimum list, and 65 % (*n*=45) would disclose even if patient preferences are unknown. Although only 7 % of respondents (*n*=5) received a report with an IF that they felt was inappropriate to return, 27 % of genetic counselors (*n*=19) feel that there are circumstances in which disclosure is inappropriate. Additionally, 75 % of genetic counselors (*n*=51) expressed great concern about storing undisclosed IF's in EMR's since another clinician may disclose unwanted information. These scenarios are likely to surface more often as WES becomes more common in clinical practice. This study suggests the clinical genetics community could benefit from guidelines on management of undisclosed IF's and from the development of infrastructure to support that process.

11p13 Microdeletion Involving Partial Deletion of *ELP4* in a Newborn Patient Without Aniridia

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Here we describe a newborn male patient born via prolonged vaginal delivery with possible right parietal fracture, seizures, respiratory distress, and hypoxic-ischemic encephalopathy. Chromosome microarray analysis (CMA) was ordered due to suspected talipes equinovarus and mildly distinctive physical features. CMA detected a heterozygous deletion at chromosome 11p13 of ~532 kilobases (kb) in size and involving 4 genes, *DCDC1, DNAJC24, IMMP1L*, and exons 1–3 of *ELP4*. Overlapping microdeletions with similar gene content have been observed in sporadic and familial aniridia patients, but have included additional *ELP4* exons with proximal breakpoints closer to the 3' end of *PAX6*. Aniridia is a congenital ocular malformation characterized by iris hypoplasia and associated ocular abnormalities. Mutations in the PAX6 gene are the most common genetic etiology of isolated aniridia. However, the ELP4 gene, which is downstream from the 3' end of *PAX6*, contains regulatory elements for *PAX6* expression. Thus, deletions involving *ELP4* but preserving *PAX6* have the potential to disrupt *PAX6* expression, and have been reported in patients with aniridia. Ophthalmology exam identified retinal hemorrhage and possible macular hemorrhage but no signs of aniridia. Following parental FISH analysis, the 11p13 microdeletion was found to be inherited from the mother, with no reported health, developmental, or vision abnormalities. To our knowledge, this patient's proximal breakpoint, ~222 kb from the 3' end of *PAX6*, is the most distal of the overlapping deletions defined by CMA in current literature. The absence of aniridia in this patient suggests that the regulatory elements for PAX6 were not impacted by this microdeletion overlapping *ELP4*. This case report adds to existing literature regarding the association between partial deletions of *ELP4* and aniridia, and emphasizes the importance of not only evaluating existing literature for overlapping gene content but considering additional molecular mechanisms when counseling patients with a copy number change detected by CMA.

Twins and Triplets and Quads, Oh My! A Review of MaterniT21 PLUS® Assay Results in Multifetal Pregnancies

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1. Sequenom Laboratories

Introduction: Since the 2011 introduction of noninvasive prenatal testing (NIPT), >400,000 clinical samples have been analyzed. Nearly 18,000 (~4 %) were from high risk multifetal gestations. The increased risk for pregnancy complications with invasive testing in this population makes NIPT a valuable screening alternative. Here we describe our clinical assay findings in a multifetal cohort. Methods: Maternal plasma samples were subjected to DNA extraction and library preparation followed by massively parallel sequencing as described by Jensen et al. Sequencing data were analyzed to detect autosomal trisomies and other subchromosomal events as described by Chen et al. Fetal fraction requirements were adjusted in proportion to fetal number. Outcome data were collected through provider solicitation. Results: The predominant indication for testing was maternal age, followed by abnormal ultrasound and serum screening. Overall positivity rates for trisomy 21 (1.5 %), 18 (0.6 %) and 13 (0.3 %) were aligned with those found in our much larger singleton pregnancy cohort of over 400,000 patient samples (1.4 %, 0.4 % and 0.2 %). Additionally, a total of 10 events associated with the Enhanced Sequencing Series (trisomy 16 and 22 and selected microdeletions) were reported in the multifetal cohort. Average turnaround time was ~5 calendar days. The non-reportable rate in this multifetal cohort was ~6 %, largely due to insufficient DNA, which is higher than our singleton cohort average of 1.6 %. Conclusion: MaterniT21 PLUS® testing in high-risk multifetal gestations has demonstrated positivity rates for trisomy 21, 18, and 13 mirroring those found in much larger cohort of singleton gestations, suggesting that the performance of the assay in multifetal gestations is comparable to that in singleton gestations, except for a higher non-reportable rate due to insufficient fetal DNA. Clinical performance concurs with expectations from the original validation studies.

Isochromosome Formation as a Rare, Recurrent Mechanism for the Occurrence of Isolated Trisomy 10p

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1. The Children's Hospital of Philadelphia

Introduction: Trisomy 10p has been reported in over 60 cases, with the majority of cases resulting from unbalanced translocation. Cases of isolated trisomy 10p are rare, with most resulting from translocation of the 10p arm to an acrocentric chromosome. Isochromosome 10p with translocation of 10q to chromosome 14p has been reported in one case with a proposed mechanism involving an exchange between chromosome 14 and the long arm of chromosome 10, followed by 10p isochromosome formation. Case Report: We report on a newborn female evaluated by genetics for multiple congenital anomalies. Prenatal ultrasounds demonstrated bilateral club feet, bilateral persistence of the superior vena cava, single umbilical artery, polyhydramnios, and possible intrauterine growth restriction. Neonatal examination was significant for sloping forehead with high anterior hairline, widely open posterior fontanelle, prominent maxilla with micrognathia, simple and slightly protuberant right ear, left ear with flattened helix and prominent antitragus, small mouth, thin upper lip with midline dip, redundant nuchal skin, right hand with a fourth digit that is wide at the base and tapers, left hand with an apparently duplicated second finger and 3–4 syndactyly, and bilateral talipes equinovarus. Chromosome analysis demonstrated a karyotype of 46,XX,i(10) (p10), der(14) t(10;14) (q10;p10). Chromosomal single nucleotide

polymorphism (SNP) array demonstrated trisomy 10p with no copy number loss detected on chromosome 10q or chromosome 14, confirming the isolated trisomy 10p. Discussion: Isolated trisomy 10p is a relatively rare chromosomal anomaly that can arise due to various mechanisms. We report a second case in which translocation of the 10q arm to chromosome 14 and formation of a 10p isochromosome gives rise to isolated trisomy 10p. This provides evidence supporting the previously proposed mechanism of chromosomal translocation followed by isochromosome formation and demonstrates that this is a recurrent, rare mechanism of chromosomal aneuploidy.

Lack of Standardization in Laboratory Reporting of Variants Outside the Coding Region: A Case Report

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A 47-year-old woman with endometrial cancer was identified as being at-risk for Lynch syndrome due to absent MSH2/MSH6 protein expression as part of universal immunohistochemical (IHC) screening. Family history was significant for ovarian cancer in her mother diagnosed at age 58. Genetic testing of the MSH2 and MSH6 genes by next-generation sequencing (NGS) technology was reported as normal by Laboratory A. At approximately the same time, her mother had genetic testing at another institution with a 25-gene NGS panel that indicated a variant of uncertain significance (VUS) in an intervening sequence (IVS), 12 base pairs (bp) downstream of exon 14 in the MSH2 gene by Laboratory B. When contacted, Laboratory A confirmed that the proband carried this same VUS in the MSH2 gene, but that it was outside the reportable range of 10 bp on either side of exon-intron boundary. A third laboratory was contacted, and it was learned that they report variants within 5 bp on either side of exon-intron boundaries. There are currently no standards for laboratories performing NGS testing with regard to reportable ranges for variants identified within an IVS. This case highlights the lack of laboratory standardization in variant reporting within the IVS region, as well as the importance of communication between families and genetic counselors to ensure appropriate interpretation. Understanding different laboratory reporting practices is crucial to providing patients with the most accurate information, particularly in families with seemingly discrepant test results. Genetic counselors should be aware of differences in variant reporting and become familiar with the policies of frequently used laboratories.

Comparing Gene Panel and Augmented Exome Tests Using a "Gold-Standard" Dataset

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1. Personalis, Inc.

Assessing the sensitivity and specificity of next-generation sequencing (NGS) based tests poses a challenge as it requires reference samples with known variants in all genomic regions that are included in the assay. Such "gold-standard" datasets have only recently been available for a subset of the genome. The Genetic Testing Reference Materials Coordination Program (GeT-RM) is a Centers for Disease Control initiative that aims to improve the availability of appropriate and characterized reference materials for genetic testing. These materials can be used by the genetic testing community for quality control, proficiency testing, test development and validation, as well as for research. In an effort to characterize the variants in reference samples, several clinical testing labs have run clinical gene panel tests on these samples and contributed their variant data to the GeT-RM. Together with data from the National Institutes of Science and Technology Genomes in a Bottle Consortium (GIAB), this data constitutes high-quality variant datasets that labs developing new NGS tests can use to assess analytical validity. We compared the gene panel test data submitted to the GeT-RM by clinical labs for reference sample NA12878, to the "gold-standard" data produced for this sample by GIAB. We also compared the results to those achieved with an augmented exome assay developed by our lab: the ACE Clinical Exome Test. Most of the panels are 100 % covered by ACE capture regions and nearly all of the remaining panels are also covered. Taken together, we found that the sensitivity and specificity of the ACE Clinical Exome Test was comparable to most gene panel tests for those genes specifically targeted in the panels. In many instances, the number of false positives and false negatives obtained was lower with the ACE Clinical Exome Test than obtained with gene panel tests. Increased standardization and transparency in reporting accuracy data for NGS tests will facilitate test selection by healthcare providers and therefore ultimately benefit patients.

Isolated Retinitis Pigmentosa and Usher Syndrome Within a Single Family

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1. Emory Genetics Laboratory

Pathogenic variants in the USH2A gene can cause isolated autosomal recessive retinitis pigmentosa (RP) or Usher syndrome type 2 (USH2). Retinitis pigmentosa is characterized by pigment deposition in the fundus, progressive visual field loss, night blindness, and abnormal or non-recordable electroretinogram. USH2 is a disorder consisting of mild to severe pre-lingual hearing loss with intact vestibular function and adolescent or adult onset RP. An individual (the proband) with a personal history of retinitis pigmentosa without hearing loss was referred to Emory Genetics Laboratory (EGL) for the comprehensive eye disorders panel. The proband's two children, child B and child C, were reported to have clinical diagnoses of Usher syndrome. The molecular results identified a pathogenic missense and a likely pathogenic splice variant in the USH2A gene of the proband. Information provided to the laboratory included previous molecular studies performed at a different diagnostic center for the proband, the proband's partner, and their children (B and C). Sequence and deletion/duplication analysis of child B identified the likely pathogenic splice variant (seen in the proband) and also a pathogenic truncating variant in the USH2A gene. Additional targeted analysis for the variants identified in individual B determined that the variants segregated with disease in child C and were found to be in trans after testing the proband and the proband's partner. The combined results showed that three different pathogenic/likely pathogenic variants were found in the same gene in a single family that in turn gave rise to different phenotypes. Initially, the proband was suspected to have dominant RP; however, it was not until further comprehensive molecular testing was performed at EGL, including the USH2A gene, that the likely cause of the proband's RP was identified.

Genetic Testing Strategies for Patients with Epilepsy and Neurodevelopmental Disorders

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1. GeneDx

Guidance is frequently requested concerning testing strategies for patients with epilepsy, given the increasing complexity of testing options. The objective of this study was to compare the positive yield of multi-gene panels for epilepsy to that of whole exome sequencing (WES). Over 5,

000 patients were tested using targeted gene panels that included next generation sequencing and exon-level deletion/duplication testing by array CGH. The panels included genes associated with both benign seizures and epilepsy with neurodevelopmental disabilities (NDD) along with subpanels for age of onset (i.e., infantile panel). WES was completed in 529 patients with epilepsy and NDD, with either just the proband (WES-Proband), or the proband and both parents simultaneously sequenced and analyzed (WES-Trio). The overall clinical sensitivity of the targeted panels was 16 % with the highest positive rate for the infantile panel (21 %, *n*=1,620). WES-Trio testing for patients with epilepsy and NDD had a positive rate of 38 % (*n*=450), which was considerably higher than the positive rate for WES-Proband, 23 % (*n*=79). The majority of autosomal dominant and X-linked disorders diagnosed by WES (83 % and 69 %, respectively) were caused by *de novo* mutations; a finding that largely accounts for the increased yield of WES-Trio compared to WES-Proband. Patients who had reflex testing to WES after a negative panel had a positive diagnostic rate of 22 % (*n*=166). Hence, reflex testing to WES-trio after a negative panel is expected to have a combined yield of greater than 40 %. These data indicate that when only a single genetic test can be ordered, WES-Trio has a considerably higher yield than a targeted panel. However, the highest clinical sensitivity could be obtained by ordering a targeted panel, with reflex testing to WES-Trio. These data may assist clinicians in determining the most effective testing strategy for a patient with epilepsy and NDD.

Mutations in *SPATA5* are Associated with a Novel Autosomal Recessive Disorder of Microcephaly, Intellectual Disability, Seizures, and Hearing Loss

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Using whole exome sequencing, we identified 14 individuals from ten independent families who have compound heterozygous or homozygous rare or novel predicted pathogenic variants in Spermatogenesis-Associated Protein 5 (*SPATA5*). Common features in these patients include microcephaly (12/13), developmental delay (14/14), seizures (13/14), hypotonia (13/14), spasticity (9/14), sensorineural hearing loss (14/14), and visual impairment (14/14, cortical in 9). Patients range from 2 to 19 years of age and have moderate to severe intellectual disability. Abnormalities on brain MRI are present in 7 out of 12 patients and include diffuse atrophy, thin corpus callosum, and hypomyelination. Short stature is present in two patients, failure to thrive in six, and immunodeficiency in four. Two patients had muscle biopsies that revealed a possible mitochondrial disorder; one patient had enlarged and abnormally shaped mitochondria and the other patient had a mild increase in subsarcolemmal and intermyofibrillar mitochondria and reduced electron transport chain activity. Generally, the patients are not reported to have dysmorphic features. *SPATA5* is a ubiquitously expressed member of the ATPase associated with diverse activities (AAA)-protein family and is involved in mitochondrial morphogenesis during early spermatogenesis, and may also play a role in post-translational modification during cell differentiation in neuronal development. Variants in *SPATA5* may affect brain development and function, resulting in the microcephaly, developmental delay and intellectual disability. Fifteen different pathogenic variants in *SPATA5* were detected in the group, including missense (9), nonsense (1), frameshift (3), splice site (1), and in-frame deletion (1) mutations. An autosomal recessive inheritance pattern is further supported by testing which indicates the unaffected parents and siblings to be heterozygous carriers or wild type. We present the first case series of patients with pathogenic variants in *SPATA5*, with phenotypic details to guide genetic counseling of families with a new diagnosis.

Expanding the Mutation Spectrum for Noonan-Like Syndrome with Loose Anagen Hair

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Background: Noonan-like syndrome with loose anagen hair (NS/LAH) is characterized by classic Noonan syndrome features such as short stature, facial dysmorphism, pectus deformities, and variable cognitive impairment in addition to more specific features including mitral valve dysplasia, darkly pigmented skin with eczema, and easily pluckable and sparse, loose anagen hair. To date, the only variant associated with NS/LAH is the recurring c.4A>G (p.Ser2Gly) variant in *SHOC2*; however, not all individuals with NS/LAH carry the p.Ser2Gly variant suggesting there is another molecular etiology. Methods: DNA samples from 39 individuals referred to our laboratory for NS/LAH were tested by either oligonucleotide hybridization-based DNA sequencing of the coding regions and splice sites of *PTPN11, SOS1, RAF1, KRAS, BRAF, MAP2K1, MAP2K2, HRAS*, and *SHOC2* exon 02 or next generation sequencing of these genes in addition to *CBL* and *SPRED1*. All variants were confirmed by Sanger sequencing. Physician-reported clinical features and molecular results of individuals with NS/LAH were compared. Results: Genetic testing identified 17 individuals (43.6 %) with NS/LAH with the recurring pathogenic p.Ser2Gly *SHOC2* variant. Interestingly, 56.4 % (22/39) of individuals tested did not carry the *SHOC2* variant and of those, 7/22 (31.8 %) carried a different established pathogenic variant in *PTPN11, KRAS, RAF1*, or *HRAS*. Furthermore, the pathogenic p.Asn308Thr variant in *PTPN11* and the p.Val14Ile variant in *KRAS* were each identified in two probands with NS/LAH. Conclusion: Pathogenic variants in *SHOC2, PTPN11, KRAS*, *RAF1*, and *HRAS* have been identified by our laboratory in individuals with NS/LAH suggesting that NS/LAH may be part of the Noonan spectrum and not a separate disorder. Supporting this, an individual with NS/LAH, who was negative for the recurrent *SHOC2* variant, carried a pathogenic *MAP2K2* variant consistent with Cardiofaciocutaneous syndrome. In addition, two individuals with Costello syndrome and loose anagen hair were found to carry a pathogenic *HRAS* variant.

Mutations in *CASK*: Challenging the Genotype-Phenotype Correlations

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Mutations in *CASK*, an X-linked gene that plays a role in brain development and synaptic function, are the cause of both microcephaly with pontine and cerebellar hypoplasia (MICPCH), and X-linked intellectual disability (XLID) with or without nystagmus. MICPCH is caused by loss of function *CASK* mutations, typically affects females, and is associated with moderate to severe intellectual disability (ID). Only a few affected males have been reported; all have had profound developmental disability. The XLID phenotype is typically caused by missense mutations and most often manifests in males; carrier females are mildly affected or unaffected. We report 7 patients with CASK mutations that expand these phenotypes and challenge the reported genotype-phenotype correlations. Cases 1 and 2 are unrelated females with loss-of-function *CASK* mutations who display a classic MICPCH phenotype. Case 3 is a female who also displayed a classic MICPCH phenotype, but was found to have a *de novo* missense mutation. Case 4 is a female with a *de novo* frameshift mutation. She has microcephaly with mild hypoplasia of the cerebellar vermis only identified retrospectively. She has ID but at age 8 can form complete sentences, expanding the mild end of the MICPH phenotype. Case 5 is a male with a *de novo* nonsense mutation who showed the severe male phenotype with intractable myoclonic seizures. He had profoundly delayed development and died at 12 months of age. Cases 6 and 7 are brothers with a maternally inherited nonsense mutation, who presented with an XLID phenotype. Brain MRI is normal in both brothers. Both are severely delayed and nonverbal. However, the oldest was walking independently at age 3 ½. Their mother is unaffected, representing the first known case of an unaffected female with a nonsense mutation. In summary, these 7 cases highlight and expand the phenotypic spectrum associated with *CASK* mutations and challenge the previously established genotype-phenotype correlations, which will impact genetic counseling for CASK-related disorders.

Exploring Attitudes of Adopted Individuals on the Utility and Value of Universal Carrier Screening

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A complete and accurate family medical history is a valuable tool to provide a thorough risk assessment. Many adoptees may not have access to this information. Carrier screening is an important aspect of reproductive risk assessment and was historically offered based on family history and ethnicity. Universal carrier screening (UCS) screens for approximately 90 genetic conditions regardless of family history or ethnicity. The study aimed to provide healthcare professionals with a better understanding of the opinions of adoptees on UCS and its potential uses. Adult adoptees were recruited through adoption organizations using an online survey. Of the 139 adoptees attempting the survey, 89 participants (75.4 %) responded they would want UCS. Participants indicated they would use results to make personal reproductive decisions (n=63), or to inform biological relatives of their risks (n=62). Many reported wanting UCS because they are curious to know their carrier status (n=76). Adoptee total household income was moderately correlated with the amount they would pay for UCS (=.327, p=0.001). There was a statistically significant difference between adoptees of differing education levels and the amount they would pay for UCS (p=0.004). In addition to providing insight into the adoptee perspective on UCS, this study also identified an important area for improvement in the delivery of carrier screening to this population. One hundred and eight participants indicated they had never been offered carrier screening (91.5 %), although the majority of adoptees would want UCS if offered. Genetic counselors are well-suited to provide UCS services to adoptees, as supported by an additional finding of the study; the majority of survey participants (84.8 %) felt a genetics professional would be helpful in undergoing UCS.

Expanded Carrier Screening is Vital in Appropriately Screening the Ashkenazi Jewish Population

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Current guidelines for individuals of Ashkenazi Jewish (AJ) descent from the American College of Medical Genetics and Genomics (ACMG, 2008) and the American Congress of Obstetricians and Gynecologists (ACOG, 2009) recommend carrier screening for 9 and 4 heritable conditions, respectively. Additional clinically severe conditions occur more frequently in the AJ population and many laboratories offer expanded AJ panels. We sought to evaluate the clinical yield of an expanded panel for persons of AJ descent and to determine the yield of enzyme analysis versus targeted mutation analysis in carrier screening for Tay-Sachs disease. Individuals underwent preconception screening at synagogues and colleges across the western U.S. in 2014 and 2015. Carrier screening was offered for those who self-identified as having at least ¼ AJ ancestry, in accordance with guidelines. The panel included all of the recommended ACOG/ACMG conditions. Screening for Tay-Sachs disease was done via enzyme and targeted DNA mutation analysis. Participants were provided pre-test information by a genetic counselor and informed consent was obtained prior to testing. Positive results were called to patients by a genetic counselor. Six hundred sixteen individuals had screening for at least 19 conditions. 27.3 % of individuals were identified as carriers of at least one of the disorders tested. Thirty eight tested positive for more than one condition. In total 197 mutations were found. The 4 disorders recommended by ACOG and 9 disorders recommended by ACMG accounted for 40.6 % (80/197) and 69.5 % (137/197) of the mutations discovered respectively. Thirty three carriers of Tay-Sachs disease were identified. 24.2 % of these were abnormal by hexosaminidase A enzyme analysis alone. Expanded carrier screening for individuals of AJ descent will identify more carriers than testing only for those disorders recommended by ACMG/ACOG. Additionally, patients who self-identify as AJ should have carrier screening for Tay-Sachs disease by both enzyme analysis and targeted DNA testing as DNA testing alone may miss at-risk patients.

A Patient-Centered Online Resource for Segregation and Reclassification of Variants of Uncertain Significance

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Multi-gene cancer panels often identify variants of uncertain clinical significance (VUS), which pose a challenge to genetic providers in managing patient's cancer risk. Family segregation studies can yield powerful data to classify VUS (as either benign or pathogenic), but resources to coordinate these studies are limited. A potential solution is to engage patients and their families in pedigree building for segregation analysis to evaluate their own VUS. For most patients including extended family members will allow VUS classification. Online genealogy and social networking tools can facilitate identifying and contacting distant relatives. We have developed an online patient-driven toolkit that teaches individuals to better understand their VUS, use available genealogy and networking resources to trace how their VUS segregates in their families, and participate meaningfully with clinical laboratories in classifying their VUS. The toolkit available at FindMyVariant.Org walks patients step-by-step through the process of classifying their variant. Modules include: 1.) What is a VUS? 2.) Co-segregation analysis for variant classification. 3.) Talking with your immediate family about your variant. 4.) Identifying ancestors. 5.) Finding and connecting with distant relatives. 6.) Laboratory testing and asking relatives to participate in VUS classification. The

free toolkit will be available to patients who have received VUS results (regardless of laboratory used) to assist them in gathering information needed to further classify their VUS. Genetics providers seek ways to make genetic information meaningful to their patients, by pointing them towards resources. We present this innovative toolkit as a resource for genetic providers to offer to motivated families. The implications of this project for the practice of genetic counseling include: expanding the availability of human genotype-phenotype correlations for rare variants in cancer risk genes and helping genetic providers empower patients to have a more active role in their genetic health.

Selecting the Best Specimen Type for Genetic Testing: A Survey of the Experience, Knowledge and Practices of Genetic Counselors

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Although peripheral blood is often considered the gold standard for genetic testing, a blood sample could give false or inappropriate testing results in several situations. For example, if an individual has an active hematopoietic malignancy or has received an allogeneic bone marrow transplantation or blood transfusion, using a blood specimen for genetic testing may result in analyzing the oncologic or donor cells instead of the intended germline cells. In order to explore whether genetic counselors recognize the importance of establishing patients' hematopoietic malignancy, bone marrow transplantation, and blood transfusion status prior to genetic testing, a web-based survey was sent to NSGC members. Respondents (n=122) were asked if they have seen patients with the abovementioned histories and if they have a process in place to elicit this information. Knowledge was assessed via several scenario- and theory-based questions. More than half of respondents reported seeing patients who had been diagnosed with a hematopoietic malignancy (n=88), or who had received a blood transfusion (n=84) or bone marrow transplantation from a donor (n=65). Up to 57 % (n=70) of respondents either did not, or did not know, if they have a process in place to elicit this information. Up to 20 % (n=24) of respondents did not know which specimen type to select in the various clinical scenarios. Approximately 17 % (n=16) of respondents were unable to correctly identify that DNA is contained in white blood cells only. This exploratory study targeted providers who are expected to be among the most informed regarding appropriate specimen selection for genetic testing. Gaps in knowledge, and a lack of consensus for approaching individuals with clinical histories that require non-peripheral blood specimens for genetic testing, were evident. Performing genetic testing on inappropriate specimens could lead to inaccurate genetic test results with significant psychosocial and medical implications.

Evidence of Aneuploid Rescue as Revealed by Circulating Cell Free DNA Testing

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Introduction:
Rescue of an aneuploidy to restore the euploid state in early embryonic development is a well-documented explanation for confined placental mosaicism (CPM). Historically, case reports have focused on the rescue of a complete trisomy or monosomy. Since the advent of prenatal chromosomal microarray, segmental CPM has also been reported, suggestive of the rescue of a partial monosomy or trisomy. Tests using circulating cell-free DNA (ccfDNA), likely derived from cells of the placenta, have demonstrated CPM as a cause for discrepancies between ccfDNA results and fetal karyotype. Case Reports: Here we report a case of a pregnancy complicated by intrauterine growth restriction (IUGR), short long bones, and abnormal serum screening, which had a normal noninvasive prenatal testing result for 21, 18, 13, X and Y. Karyotype on amniocytes was 46, XY,inv (2) (p11.2q13) and subsequent single nucleotide polymorphism (SNP)-based array showed maternal uniparental heteroisodisomy of chromosome 2, suggestive of a rescue event in the placenta. Evaluation of ccfDNA sequencing traces of chromosome 2 was also suggestive of trisomy 2, consistent with a trisomy rescue in the placenta. We also report the suspected rescue of a 1p36 microdeletion in a patient who had ccfDNA testing and a follow-up amniocentesis which demonstrated complete homozygosity along the region originally detected by ccfDNA to contain a deletion. This pregnancy was further complicated by premature rupture of the membranes at 23 weeks gestation and birth of a premature infant with features of Goldenhar syndrome at 25 weeks gestation. Discussion: These cases may represent a complete trisomy rescue as well as a segmental monosomy rescue event detectable by ccfDNA. CPM of an aneuploidy can lead to complications in pregnancy, including IUGR and premature delivery. There is not enough data to determine whether a similar effect can be caused by CPM of a segmental rescue. Additionally, aneuploidy rescue and segmental rescue can lead to uniparental disomy (UPD) or partial UPD, in some cases causing an imprinting error in the fetus.

The Usage of Existing Practice Guidelines may miss Half of Pathogenic Mutations in Hereditary Cancer

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Background: Genetic Counselors have expertise in identifying phenotypes associated with known hereditary cancer syndromes. Existing practice guidelines from the American College of Medical Genetics and Genomics, NSGC, National Comprehensive Cancer Network, and the Amsterdam Criteria inform genetic testing strategy. With the recent widespread uptake of clinical next-generation sequencing (NGS), laboratories analyze dozens of hereditary genes simultaneously using 'panel testing.' Objective: The goal of this study was to determine whether the existing practice guidelines are adequate to guide clinical genetic testing by assessing results from 16 month's experience with hereditary cancer panel testing at the Medical College of Wisconsin. Methods: We undertook a retrospective analysis of the results from panel testing from 321 patients. Results: Half (18/36) of the pathogenic mutations detected would have been missed if single gene testing was done as recommended in current practice guidelines using phenotype. Of those patients found to have a pathogenic mutation who met hereditary breast and ovarian cancer testing criteria, only 53 % (9/17) had a BRCA1 or BRCA2 gene mutation. Conversely, 47 % (8/17) of those who had a pathogenic mutation and met testing criteria had mutations in genes other than *BRCA1* and *BRCA2*, and would have been missed if panel testing had not been done. Conclusion: Our results suggest that the current model of phenotype driven single gene testing based on practice guidelines is insufficient to obtain a genetic diagnosis in hereditary cancer. The use of comprehensive panel testing nearly doubles the identification of pathogenic mutations. The existing definitions of some hereditary cancer syndromes require re-consideration as the use of panel testing has led to the discovery of a broader phenotypic

spectrum. Our findings contribute to further understanding of the utility of panel testing in cancer genetics and provide evidence to guide genetic counseling practice in the offering of expanded genetic testing.

APOE Genotyping: Are We Ready for Clinical Use? A Survey of Physicians

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Research on the effects of traumatic brain injury (TBI) has drawn a spotlight to the issue of TBI among athletes. *APOE* genotype is a risk factor for poor recovery from TBI, and may be useful to athletes considering participation in sports with a high incidence of TBI, or for doctors in care of TBI. Clinical use of *APOE* genotyping is often discussed in relation to its association with risk for late-onset Alzheimer disease (LOAD). Testing is generally discouraged, in part because the information is not medically actionable. Personalizing the risk of poor recovery from TBI has more clinical value; however, it may also raise the risk of genetic discrimination. In order to explore the perceived clinical value of *APOE* genotyping for this purpose and the obstacles to its use, we surveyed 233 physicians involved in the treatment of athletes with TBI contacted through the list serve of the American Medical Society for Sports Medicine. Results suggest that they are open to using *APOE* testing, with 62.2 % (n=148) saying that they would always or frequently offer a test that could predict poor recovery from TBI to athletes interested in participating in sports with a high incidence of TBI, and 37.8 % (n=89) saying they would always or frequently order such a test when making a plan for return-to-play. However, they are apprehensive about offering *APOE* testing, and most likely to identify the risk that the results might interfere with their patient's athletic career as the issue of presumed greatest concern to their patients (60.9 %, n=145), and the biggest obstacle to clinical use in their practice (53.2 %, n=126). Physicians expressed concern about their readiness to counsel patients for the genetic risks associated with LOAD, and 37.4 % (n=89) described themselves as "not familiar" with the relationship between *APOE* and LOAD. Given a choice of methods for educating patients, the majority chose the option of genetic counseling (51.3 %, n=122) and most (64.3 %, n=153) said they would be more likely to order genetic testing if they could refer their patient to a genetic counselor.

Assessing Test Quality in a Rapidly Changing Genetic Testing Landscape

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In recent years, across clinical subspecialties of genetic counseling, options for genetic testing have grown at an unprecedented rate. Evaluating and comparing genetic tests has become an increasingly time consuming and complex part of genetic counseling practice. One of the most complicated aspects of this process lies in assessing the quality of the testing and accompanying services provided by laboratories. Quality of testing can be assessed in a number of ways, ranging from laboratory certifications to variant level analytic and clinical validity data. These data are currently presented by laboratories in a variety of ways and test sensitivity is represented differently by various laboratories across different types of tests. Quality of services includes attributes such as meeting the stated turn-around time, expertise of laboratory staff, reporting and documentation process and accessibility of customer service personnel to ordering clinicians. While genetic counselors frequently cite quality of services as a major factor in choosing a laboratory, this concept can be challenging to address objectively. Our working group of clinical and laboratory genetic counselors, formed in response to a lack of clear guidelines on this topic by members the Test Utilization Subcommittee of the Industry SIG, will present our taxonomic framework and discussion points for assessing laboratory quality and identifying high quality tests for patients. Genetic counselors have a strong history of serving on the front lines of evolving and growing fields. Laboratory and test selection is an area of increasing complexity and it is critical that genetic counselors take a leadership role in this rapidly changing landscape.

Ophthalmologists' Perspectives on and Utilization of Genetic Testing

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Genetic testing (GT) has the potential to benefit patients with inherited ophthalmic conditions, however our understanding of its use by ophthalmologists is limited. This exploratory study examined providers' perspectives on ophthalmic GT. Based on previous research on GT in other medical specialties, we developed a 46-item on-line survey examining demographics and GT-related variables included experiences, knowledge, comfort with the process, perceived utility, and barriers/facilitators to ordering GTs. Participants included ophthalmologists (MDs) who were either alumni of our academic medical center or members of the National Eye Institute eyeGENE consortium. Having experience or no experience ordering GT was used to dichotomize respondents. Group differences related to the variables were analyzed using either chi-square or t-tests. Significant variables were entered into a logistic regression using GT experience as the binary outcome. Seventy-two MDs responded to the survey, 52.7 % had ordered GT. Significant differences (p<=0.05) between groups were found based on clinical specialty, work setting, training, patient race, patients seen per year, perceived utility of GT, self-reported knowledge of genetics, and comfort with the process. In the regression, personally having had GT done (p=0.015), patients asking about GT (p=0.004), and comfort with the GT process (p=0.002) were each positively associated with ordering GT. These results highlight the fact that the reasons ophthalmologists use GT may be driven by non-medical physician- or patient-related factors rather than clinical utility. Ophthalmologists consistently ranked diagnostic use of GT as more important than other uses including determining inheritance, prognosis, and use for potential clinical trial enrollment. This ranking of perceived GT value suggests that ophthalmologists have limited recognition of the extent to which it can benefit patients. Our study is generally consistent with previous work examining other groups of physicians, with the novel finding that personal experience with GT can impact its utilization.

SNP Array: Valuable Tool to Guide Targeted/Accurate/Cost Effective Diagnosis of Autosomal Recessive Conditions

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1. All Children's Hopital

Microarray analysis is the first tier genetic test for patients with unexplained intellectual disability and/or multiple congenital anomalies.

Single nucleotide polymorphism (SNP) arrays detect imbalance and copy neutral loss of heterozygosity (LOH), providing information about uniparental disomy (UPD) and consanguinity. Targeted strategies for molecular testing, guided by SNP array results, are illustrated by 4 patients diagnosed with autosomal recessive (AR) disorders. Case 1: Neonate with *situs inversus totalis*, cough, congestion, respiratory distress; SNP array revealed 781Mb of LOH, coefficient of inbreeding (F) = 0.25, first degree consanguinity. 10 genes associated with situs inversus within LOH regions included 6 genes for primary cililary dyskinesia (PCD). Abbreviated 6 gene PCD panel detected homozygous *DNAAF2* pathogenic variant, PCD type 10. Case 2: 14 year male, abnormal electromyography, consistent with demyelinating neuropathy. 341 Mb LOH found by SNP array, F = 0.109, second degree parental relationship. 191 AR conditions within LOH regions included a demyelinating neuropathy, Charcot Marie Tooth disease, type 4C (CMT4C), caused by variants in SH3TC gene. Molecular analysis of *SH3TC* (instead of full CMT panel) demonstrated homozygous pathogenic variant. Case 3 and Case 4 both had LOH with F = 0.0126, fifth degree parental relationship. Case 3: Neonate with status epilepticus, intractable epilepsy, responsive to pyridoxal-5 phosphate (form of vitamin B). SNP array showed 40Mb of LOH including PNPO gene associated with pyridoxamine 5'-phosphate oxidase deficiency. Molecular analysis of *PNPO* (instead of full epilepsy panel) identified homozygous pathogenic variant. Case 4: Neonate, with zero Screening Test for SCID: T-cell Receptor Excision Circles (TREC) on newborn screen; diagnosed with T-, B+, NK+ severe combined immunodeficiency (SCID). SNP array detected 51Mb of LOH, including IL7R gene associated with this same type of SCID. Homozygous pathogenic variant in *IL7R* was identified and absent IL7R expression by protein function confirmed diagnosis. SNP analysis is an effective tool enabling cost effective, targeted molecular testing and expediting diagnosis.

A Case of Salt-Wasting Congenital Adrenal Hyperplasia Resulting from Two De Novo Mutational Events in *CYP21A2* in Two Generations

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Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive condition caused by mutations in the CYP21A2 gene. 21-hydroxylase deficiency is the most common form of CAH and can be subdivided into three forms, the most severe of which is salt-wasting (SW) CAH. A significant proportion of CAH mutations result from recombination events between *CYP21A2* and a highly homologous pseudogene (CYP21A1P) located 30kb upstream. These recombination events, and a *de novo* rate of about 1 %, present unique challenges for genetic testing laboratories. In order to provide a more accurate and comprehensive analysis of this complex region, it is important to perform copy number analysis of *CYP21A2*, *CYP21A1P* and the hybrid alleles formed due to recombination events, along with full gene Sanger sequencing of *CYP21A2* and of potentially active hybrid alleles. We present the case of a Saudi Arabian child affected with SW CAH and no known family history. Analysis revealed two copies each of *CYP21A2* and *CYP21A1P.* Sequencing of *CYP21A2* revealed three SW mutations: p.I236N, p.V237E, p.M239K and a novel frameshift mutation, c.558_562delCTTAA, p.L186AfsX107. The first three mutations are commonly inherited in *cis* and referred to as the exon 6 cluster. Parental studies revealed the exon 6 cluster was paternally inherited and p.L186AfsX107 resulted from a *de novo* event. Full gene sequencing and segregation analysis of multiple benign variants confirmed that the *de novo* event occurred on the proband's maternally inherited allele. Studies of the proband's paternal grandparents revealed the exon 6 cluster occurred as a *de novo* event on the proband's father's maternally inherited allele. This report demonstrates how two *de novo* events in one family resulted in a case of SW CAH, and illustrates the usefulness of combining parental studies and full gene sequencing in cases of *de novo CYP21A2* mutations. This case also supports the use of full gene sequencing rather than targeted analysis of common mutations, which would have missed the de novo frameshift mutation.

Genetic Testing Outcomes for Hearing Loss in a Multidisciplinary Hearing Clinic Setting

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Congenital hearing loss occurs in 2–3 per 1,000 babies in the United States. It is estimated 50 % of congenital hearing loss (HL) is genetic and when genetic, is highly heterogenous. Previously, genetic testing was limited to single gene testing, namely *GJB2/GJB6*. However, with the advent of next generation sequencing platforms, conditions like HL are prime targets for maximizing the full diagnostic potential of this technology. In the state of Colorado, there are two multidisciplinary clinics focused solely on hearing loss. Specialties participating in these clinics include audiology, otolaryngology, genetics, speech pathology, developmental specialist, and family support. Since multigene panels became available, 152 individuals pursued this testing through these clinics and the general genetics clinics. Testing was offered to all children with congenital or childhood onset hearing loss that was bilateral in nature. Majority of individuals had no other health or developmental concerns separate from their hearing loss. Genetic counseling was provided before sample collection and again when results were reported out. Two different panels were offered to families: OtoSCOPE® from Univeristy of Iowa (66–116 genes) and OtoGenome® from Harvard-affialiated Laboratory (71 genes). Of the 152 individuals who pursued testing, results are available for 140 to date. A genetic etiology was identified in 52 % (73) and no etiology was identified in the remaining 48 % (67). Positive results included: 50 % *DFNB1*, 12 % *DFNB16*, 10 % Usher, 10 % *DFNA17*, 12 % miscellaneous AR genes, and 6 % miscellaneous AD genes. Previous testing strategies using single gene testing yielded a positive result in about 5-10 % of cases. These data argue that the use of multigene panels allow for significantly improved detection rates in congenital and childhood onset hearing loss which in turn results in better prognostic information and directed improved medical management guidelines for these families.

Whole Exome Sequencing Identifies the first *PANX1* Germline Mutation in an Individual with Intellectual Disability, Hearing Loss, Endocrine Dysfunction, and Skeletal Abnormalities

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A 17-year-old female patient was referred for clinical genetic testing due to a suspected diagnosis of Perrault syndrome. She exhibited intellectual disability, sensorineural hearing loss, premature ovarian failure, and skeletal abnormalities including delayed bone age, short stature, and kyphosis. Utilizing a whole exome sequencing platform, targeted analysis of five genes associated with Perrault syndrome (*CLPP, LARS2, HARS2,*

HSD17B4) and Woodhouse-Sakati syndrome (*DCAF17*) was performed. When no pathogenic variants were identified in these five genes, analysis of the whole exome was performed using the previously generated data, and a homozygous missense mutation (c.650G>A) in *PANX1* was identified. This mutation results in a conservative amino acid substitution of arginine to histidine at position 217 (p.R217H) of the protein. The parents, who were reported to be first cousins, were both heterozygous for the R217H mutation. *PANX1* encodes pannexin1, an ATP release channel with both structural and functional similarities to the connexin gap junction proteins. *PANX1* is highly conserved across species and is ubiquitously expressed, with robust expression in many regions of the brain, including the cochlea. Dye uptake, ATP release, and electrophysiological measurements revealed R217H to be a loss-of-function mutation. This is the first report of a human germline *PANX1* pathogenic mutation, implicating *PANX1* in this newly described form of syndromic hearing loss, and underscoring the efficacy of whole exome sequencing in the identification of novel disease-associated genes.

A Rigorous Approach for Evaluating the Importance of Sanger Confirmation of Next-Generation Sequencing Findings: A Call for Collaboration

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1. Invitae
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Many laboratories use next-generation sequencing (NGS) to detect clinically significant germline variants. Positive test results can lead to substantial medical decisions, and it is imperative that genetic tests have high specificity and PPV (positive predictive value). Thus, high-quality clinical labs, including our own, confirm NGS findings using a second, orthogonal method, such as Sanger sequencing.
While some NGS methods have high false-positive rates, improvements in sequencing chemistry and bioinformatics can provide excellent specificity without sacrificing sensitivity. We examined all 3,105 variants detected by NGS in our lab to date that (a) passed stringent NGS quality control, and (b) had orthogonal data available. All 3,105 were confirmed with zero false positives. Nevertheless we continue confirmations, which of course add turn-around time and cost. Other NGS laboratories have also made similar observations. We propose a rigorous framework for evaluating the importance of confirmation in different cases, separating situations where it is even possibly beneficial (e.g., around many indels) from situations where a substantial data set clearly demonstrates that confirmation adds little value. We assign statistically meaningful "worst case" estimates to false positive rates, which may aid in careful decision making on this subject. Genetic counselors must become intimately involved in this conversation. Patient safety is critical, as is patient and provider confidence in genetic test results. In question here is (a) how much data would be enough to change both practices and perceptions regarding confirmatory testing; (b) what specific criteria distinguish labs which meet a strong NGS performance standard from those which do not; (c) how do we best explain these considerations to patients and non-genetics professionals. Our data suggest, but certainly do not determine answers which can only come from ongoing dialog and leadership within the clinical GC community.

Pan-Ethnic Carrier Screening for Cystic Fibrosis: A Call for a Standardized Expanded Mutation Panel

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1. Recombine
2. USC Keck School of Medicine

Introduction: Carrier screening for cystic fibrosis (CF) is recommended for all individuals regardless of ethnicity. The American College of Medical Genetics and Genomics recommends a 23-mutation panel, which has limited detection rates outside of the European population. Thus, expanded screening for additional mutations has become more common. To determine the clinical utility of expanded CF screening, we assessed the rates of CF carriers across ethnicities and across varying panels. Methods: Informed consent was obtained to use genetic data from expanded carrier screening results for 5,272 patients. Inclusion was limited to patients who reported a single ethnicity. 108 CF mutations were tested in this assay. Heterozygous calls for each mutation were tallied by ethnic group, and respective carrier rates were determined. Carrier rates were also calculated for each ethnic group using only data from the ACMG recommended 23-mutation panel as well as the commonly used 32- and 97-mutation panels. Data were compared across ethnicities and across panels. Results: A total of 16, 19, 35, and 41 mutations were identified in our patients out of the 23, 32, 97, and 108 possible mutations. It was determined that 23 %, 21 %, and 7% of carriers were missed by the 23-, 32-, and 97-mutation panels when compared to the 108-mutation panel. As expected, carrier frequencies seen across ethnicities increase gradually with the size of the panel. Carrier rates in the two smaller panels are highly comparable across ethnic groups, with the exception of Middle Eastern individuals, which increased from 1/92 to 1/46. The same is true of the larger panels, with the exception of Asian individuals, which increased from 1/135 to 1/45. Conclusions: Our results show that the currently recommended 23-mutation panel missed 23% of carriers identified within our patient population, indicating this panel may not be appropriate for pan-ethnic CF carrier screening. Given this, implementation of a standard expanded CF panel incorporating mutations common in non-European individuals should be considered in order to provide comprehensive patient care.

A Unique Finding of Somatic Mosaicism for a Novel Mutation in the Already Rare X-Linked Joubert Syndrome

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Joubert syndrome is a disorder characterized by the cardinal features including a distinctive cerebellar and brain stem malformation known as the molar tooth sign, hypotonia, and developmental delays. There have been 19 genes identified to be associated with this condition. Included is the gene *OFD1*, which is associated with a rare X-linked recessive form of Joubert, with only three families reported in the current literature. Affected males with reported *OFD1* mutations had variable phenotypes including the classic features as well as postaxial polydactyly, retinal disease, renal cystic disease, hydrocephalus, and occipital encephalocele. We introduce a 3-year old %Caucasian male who presented to genetics with overall delays and MRI revealing a molar-tooth sign. He had hypotonia, noted since birth. He was macrocephalic with his head measurement greater than the ninety-seventh percentile. Birth and pregnancy history were reported to be normal. At age 3 he could walk approximately 3–4 steps independently with a wide-based gait. He had a normal renal ultrasound. Molecular testing using a Joubert gene panel identified a variant of uncertain clinical significance in the X-linked OFD1 gene. This variant, c.533T>C, is predicted to result in the amino acid substitution p.Leu178Pro. This variant has not been reported in the medical literature; whereas all other pathogenic changes in *OFD1* noted to cause Joubert syndrome are frameshift, nonsense, or splice site mutations. This patient's genetic change is a missense mutation. Also unique to this case is that his mutation was only present in about 15 % of the blood cells sequenced. To further investigate, a different cell line was analyzed; targeted analysis on buccal cells again showed mosaicism for the same variant seen in the

blood. The patient's mother was tested and she was found to be negative, suggesting this *de novo* mutation is pathogenic for disease, and occurred postzygotically leading to somatic mosaicism. To our knowledge, this is the first report of such an occurrence in X-linked Joubert syndrome.

Anticipation, Ancestry, Anxiety and Autonomy: Adoptive Mothers' Views on Genetic Testing of Their International Adoptees

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Families with adopted children present unique challenges for genetics professionals. Family history is often missing for adopted children, thus limiting information on inherited genetic risks. Genetic testing presents as an opportunity for adoptive families to answer family history and ancestry questions. Little is known, however, about adopted parents' views on genetic testing. This study aimed to explore reasons parents of adopted children choose or do not choose genetic testing, as well as their perceptions of benefits, limitations, and uses of genetic testing. Seventeen parents, recruited from two international adoption support groups, completed a survey containing questions about their history of genetic testing. Of these, seven parents (all from different families) participated in semi-structured, phone interviews exploring their views and opinions of genetic testing of adopted children. Two parents had chosen genetic testing for their children; five had not. Inductive analysis yielded several themes. Reasons for testing one's children (n=2 parents) included: current medical need, and desire for ancestry information. Reasons for not choosing testing (n=5 parents) included: no current medical need, maintaining child's autonomy, and unforeseen consequences of testing. Across the sample, perceptions of benefits and uses of genetic testing results in adoptive families included: understanding the child's medical concerns, informing the child's identity, connecting with biological relatives, predicting future disease, and helping the child/family prepare for their medical future. Perceptions of limitations included: cost, anxiety/worry, unforeseen consequences, and sacrificing the child's autonomy. Implications of the findings for genetic counseling practice (e.g., suggestions regarding content of discussions about genetic testing with adoptive families) and recommendations for future research are discussed, especially in regards to predictive testing. This study adds to the growing literature on genetic testing in adoptive families.

Increasing the Diagnostic Yield from an Eye Disorders Panel: What can Clinical Genetics Professionals Do to Get the most for Their Patient

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The comprehensive eye disorders panel at Emory Genetics Laboratory is an analysis of almost all clinically relevant genes associated with syndromic and non-syndromic inherited retinal and choroidal dystrophies. There is a wide range of genetic and phenotypic heterogeneity in these disorders and molecular studies may aid in establishing a clinical diagnosis. The following two cases offer examples of how the diagnostic yield can be increased. The first case describes an individual with retinal detachment, pigmentary retinal changes, and a clinical suspicion of Wagner syndrome. Initial sequence analysis was inconclusive with 3 variants of unknown significance detected in genes unrelated to the phenotype. Subsequent deletion/duplication analysis of the genes on the panel identified a deletion of exon 8 in the VCAN gene. To our knowledge, this is the first single exon deletion described in the VCAN gene. Previously Wagner syndrome had only been attributed to splice variants that give rise to loss of exons 7 and/or 8. This case expands the reported mutational spectrum of Wagner syndrome and highlights the importance of utilizing deletion/duplication studies following a negative sequencing panel, even when a whole/multiple exon deletion or duplication has not been previously described. The second case describes an individual referred for optic atrophy. An apparently homozygous variant in the WFS1 gene was identified which had previously been reported but with insufficient evidence to classify as pathogenic/likely pathogenic. Additional clinical information was provided by the referring physician which included specific features seen in Wolfram syndrome in the individual. As a result, given all of the evidence, including the current case, the *WFS1* variant was classified as likely pathogenic. This case highlights the importance of providing comprehensive clinical information, even if it is not believed to be relevant to the initial clinical suspicion. These cases demonstrate two ways in which additional analysis or clinical information helped increase the diagnostic yield.

Zero to Four: How many AGG Interruptions are Commonly Seen in *FMR1* Intermediate and Premutation Alleles?

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1. Natera, Inc.
2. Asuragen, Inc.

Objective: Report the number of AGG interruptions (AGGs) in FMR1 intermediate and premutation alleles in a general female carrier screening population. Purpose: Assess the overall likelihood for a change in risk for FMR1 allele expansion based on the number of AGGs. Methods: Retrospective review of 13,478 Fragile X carrier screening samples received at a lab for analysis. *FMR1* CGG repeat testing was performed using a PCR based method. 357 samples (273 with intermediate and 84 with premutation alleles) were sent to a second lab for reflex testing performed via a Clinical Laboratory Improvement Amendments (CLIA)-validated test that utilizes AmplideX® GC-rich PCR chemistry in a novel amplification format to reveal the number and position of AGG interspersions and deduce the comprehensive *FMR1* genotype. For cases with premutation alleles, analysis was performed to determine the change in risk for expansion to a full mutation as compared to prior published studies. Results: The number of AGGs in intermediate and premutation alleles ranged from 0 to 4: 23 (6.4 %) had 0 AGGs; 106 (29.7 %) had 1 AGG; 206 (57.7 %) had 2 AGGs; 10 (2.8 %) had 3 AGGs; 12 (3.4%) had 4 AGGs. Of 22 samples with 3 or 4 AGGs, only one was associated with a premutation allele. Of all samples with premutation alleles: 73 (86.9%) had at least 1 AGG; 80% had reduction in ris %k for expansion to a full mutation (ranging from 1.3 to 30 %); 19 % had increase in risk for expansion to a full mutation (ranging from 0.3 to 36%); 1% had unchanged risk for expansion. Conclusions: Intermediate and premutation *FMR1* alleles largely had 1 or 2 AGGs. Intermediate alleles had a higher average number of AGGs compared to premutation alleles, which may explain their stability during transmission to offspring. 99% of cases with a premutation allele had a change in risk for expansion to a full mutation based on AGG results. This data underscores the importance of AGG interruption testing for refining risk for *FMR1* allele expansion.

Parental Testing for Variants of Unknown Significance: Is it worth it?

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Genetic testing using large gene panels has become the norm. Panels can range from having as few as three genes to having over one hundred

genes. A frequent concern is the burden of detecting variants of unknown significance (VOUSs). Parental testing is often recommended to help determine the clinical significance of VOUSs. This study examines the impact of parental testing on reclassification of variants. Using data available from Emory Genetics Laboratory, we performed a pilot study to determine how often testing parental samples allowed reclassification of a variant. A comparison of 144 neurology panel (50 genes) cases and 144 autism panel cases from 2014 was performed. Interestingly, 14 neurology and 53 autism cases were negative with no variant being reported. There were 14 neurology cases with a pathogenic variant of which the variant was diagnostic in 10 and 11 autism cases that had at least one pathogenic variant with the variant being diagnostic in 6 cases. In cases where VOUSs were identified, parental testing was performed in 41/116 neurology cases and 21/80 autism cases. Of those with parental testing, 7/41 neurology cases and 7/80 autism cases had variants that were recla %ssified.
Of the reclassified cases, 4/7 neurology had VOUSs that were reclassified to likely pathogenic compared to 2/7 amongst the autism cases. There were 4 neurology and 1 autism case in which parental testing allowed reclassification to pathogenic after sample identity testing. In 3/7 neurology and 5/7 autism cases, a variant was reclassified as likely benign after parental testing. This pilot study revealed the impact of parental testing on reclassification of variants. By looking at a larger number of cases and other panels we will determine the utility of parental testing based on well-defined versus non-specific phenotype; whether variants are in genes for autosomal recessive, autosomal dominant or X-linked disorders; or is gene-specific.

Rare and Novel Cystic Fibrosis Variants are Prevalent in Pan-Ethnic Populations

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1. Good Start Genetics, Inc.

Objective: To assess the types and frequency of *CFTR* variants in a pan-ethnic population using next-generation sequencing (NGS). Design: NGS-based carrier screening was used to screen for the presence of pathogenic *CFTR* variants. Materials and Methods: The *CFTR* coding region and intron-exon borders were sequenced by NGS in a pan-ethic population of 53,396 individuals referred for carrier screening from fertility centers across the U.S. Both previously known and novel truncating variants were considered pathogenic. Self-reported ethnicity data were collected. Results: Out of 53,396 patients, 1,834 carriers of 136 unique *CFTR* variants were identified, resulting in an overall carrier frequency of 1/29. The carrier frequency in males was higher than in females (1/23 versus 1/31), likely due to a high rate of infertile males (CAVD) in our dataset. 1,049 patients were carriers of delF508. Of the remaining 135 unique variants, 74 were identified in only one individual each, representing 8 ethnicity demographics, including ethnicity not provided. Additionally, 11 of these 74 were novel truncating variants, detectable only by sequencing. Conclusions: In pan-ethnic populations, there is a high frequency of rare and novel pathogenic variants. Even for a well-characterized disorder like cystic fibrosis, traditional carrier screening via genotyping would have missed ~50 % of the variants we detected by NGS. Cystic fibrosis screening by NGS will identify more carriers than traditional genotyping across all ethnicities.

Next-Generation DNA Sequencing: Improving the Accuracy of Routine Carrier Screening

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1. Good Start Genetics Inc.

Objective: To evaluate the efficacy of next-generation sequencing (NGS) versus traditional genotyping for routine carrier screening for guideline recommended disorders based on the frequency of carriers that would not have been identified by genotyping alone. Design: An increasing number of physicians screen all patients, regardless of ethnicity, for the same disorders because it is difficult to ascertain a patient's ethnicity to offer appropriate ethnicity-based carrier screening. Up to 13 Ashkenazi Jewish (AJ) tests are frequently ordered in patients who do not identify as AJ. Consequently, many low-risk patients receive genotype-based screening with low or unknown detection rates. In contrast, since NGS captures a larger variant set, carrier status should be more accurately determined, even in low-risk patients. Materials and Methods: Using NGS, carrier status was evaluated for up to 13 society-recommended AJ genetic disorders in fertility centers in the U.S. Cystic fibrosis was excluded from this analysis because screening is recommended for all patients regardless of ethnicity. Results: 64,584 patients from a wide range of ethnicities had screening. 1,012 carriers (of 259 distinct variants) were detected. In this population, 1 in 64 patients were identified as a carrier of at least one disorder tested. 30 % of carriers would have been missed by traditional genotyping assays. Of the 1,012 carriers, only 16 % identified as high-risk (i.e., AJ). Of the 84 % of carriers who did not identify as the "high-risk", 471 identified as low-risk and 378 did not provide an ethnicity. Had traditional genotyping been used, 37 % (175) of carriers would have been missed in the low-risk group, 35 % (131) in the group that did not provide ethnicity, and 1.2 % (2) in the high-risk group. Conclusions: Carrier screening with traditional genotyping misses a significant number of carriers, in both high- and low-risk populations. NGS more thoroughly evaluates carrier status, regardless of patient ethnicity.

Benign Variants in *HEXA* Account for Enzyme Positive Results for Tay-Sachs Disease Carrier Screening in African Americans

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1. Good Start Genetics, Inc.

Tay-Sachs disease (OMIM 272800) is an autosomal recessive disorder caused by pathogenic mutations in the HEXA gene. Carrier screening for Tay-Sachs disease is recommended for the Ashkenazi Jewish population and certain other high-risk ethnic groups. Screening consists of HexA enzyme analysis and/or DNA analysis of the HEXA gene. According to professional societies (including the American College of Obstetricians and Gynecologists), enzyme analysis should be used to screen individuals in low-risk populations, as their mutations are less likely to be included on targeted DNA genotyping panels. Using our high-throughput Next Generation sequencing platform, it is possible to efficiently sequence the HEXA gene and identify common founder mutations, as well as rare and novel alleles. Here we present an in-depth comparison of DNA sequencing and enzyme-based carrier screening of Tay-Sachs disease in 8,148 individuals of various ethnicities. Our findings show that mean percent HexA enzyme values are lower in African American (AA) individuals as compared to non-AA populations. Enzyme-based screening yields more AA carriers than would be predicted by the incidence of Tay-Sachs in the AA population, strongly suggesting false positive enzyme results. Next we show that two benign variants, prevalent in AA populations, are associated with reduced enzyme activity in African Americans. Over half of enzyme positive, DNA negative AA samples in our dataset are heterozygous or homozygous for at least one of these variants. These results strongly suggest that carrier screening via enzyme analysis is of limited utility in AA populations. Therefore carrier screening by DNA sequencing, with a more comprehensive panel of mutations

(versus genotyping), is expected to be the most accurate means to determine carrier status.

Genetic Counselors' Current Practices, Challenges and Needs for Support with Clinical Exome and Genome Sequencing

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Exome and whole genome sequencing (ES/WGS) have become increasingly incorporated into clinical practice as useful diagnostic tools for patients who have not had success with traditional genetic testing methods. At many institutions, genetic counselors (GCs) play a central role in ordering and disclosing results from genomic tests and are uniquely qualified to address some of the inherent challenges that have accompanied the rapid emergence of genomic technologies. An anonymous online survey was conducted to investigate these challenges and elucidate specific areas where support is needed. The survey was distributed through the American Board of Genetic Counseling and the National Society of Genetic Counselors. 220 GCs submitted surveys for analysis, of whom 77 % currently utilize ES/WGS in clinical care. In general, complexity of informed consent, results disclosure, and needs for support are all greater for ES/WGS than for other types of genetic testing. GCs who had been utilizing ES/WGS for less than 2.5 years were more likely to rate all three as 'significantly more' complex ($p<0.05$). GCs reported needing the greatest amount of support with variant interpretation and medical management related to both primary and secondary results. Those not yet involved with ES/WGS anticipated significantly higher needs for support than individuals who currently use it ($p<0.05$), except with regard to interpretation and medical management of primary results. Coding of qualitative data from open-ended items revealed trends related to unequal access to ES/WGS as a result of lack of insurance coverage, differences in provider thresholds for ordering testing, and lack of established eligibility criteria. Institutional support services related to assessment of candidate patients, variant interpretation, and education of non-genetics providers would improve equality of patient access to testing and consistency in patient care. Ultimately, this would be beneficial for GCs and other providers involved in ES/WGS as its scope and utilization across specialties continues to increase.

The Integration of the American College of Medical Genetics and Genomics Interpretation of Sequence Variants Guidelines in Clinical Variant Analysis and Interpretation Processes: A Model for Diagnostic Standardization and Classification

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1. Invitae

Recently, the American College of Medical Genetics and Genomics (ACMG) published updated guidelines for the interpretation of sequence variants (ISV), which represent a major step towards the standardization of evidence assessment and variant classification among diagnostic labs. Since variant classification plays a critical role in patient counseling and decision-making processes, as well as in treatment and management protocols, the published guidelines aim to provide genetic counselors and physicians with consistent and high-quality clinical laboratory services. Here we present "Sherloc," a weighted, score-based classification system based on the elements described in the 2013 draft ISV guidelines. It has been refined over 2 years of use and optimized for accuracy, efficiency, and reproducibility. Sherloc adds greater resolution to broad ISV rules that encompass various use cases, adds dependencies between rules to reduce redundant use of evidence, and incorporates detailed usage notes for various evidence types. To evaluate the concordance of this classification system with current community standards, we compared classifications of more than 800 variants to a consensus classification derived from ClinVar submissions. Sherloc classifications were very often (92.2 %) in the consensus majority; indeed, more so than ClinVar submissions from other diagnostic labs when benchmarked equivalently (85.7 %). Most differences between Sherloc interpretations and the consensus were modest (e.g., between likely pathogenic and pathogenic or between likely benign and benign). We selected 42 variants for which Sherloc-based interpretations were discordant with the consensus and re-interpreted them using a different internal analyst who was blinded to the original interpretation. Although these variants were enriched for "difficult-to-interpret" cases, a high percentage (92.5 %) resulted in the same classification by a new scientist, demonstrating remarkable reproducibility. Our implementation of Sherloc illustrates the practical application and evolution of ISV criteria in a highly scalable clinical molecular lab setting.

Clinically Significant Variants Detected Via Whole Genome Sequencing and Reported in a Large Healthy Adult Cohort: Clinical Utility and Pre-Test Counseling Implications

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1. Illumina

Background: Since May 2012, the Illumina Clinical Services Laboratory (ICSL) has performed clinical whole genome sequencing (cWGS) on 538 healthy adults for predisposition and carrier screening.
Methods: Individuals were evaluated as part of a cWGS test that included 1,600 genes associated with 1,221 monogenic conditions (n=443) or as part of an expanded test that encompasses 1,691 genes associated with 1,232 monogenic conditions (n=95). Evidence was evaluated by a team of geneticists and genetic counselors and variants were classified according to the American College of Medical Genetics and Genomics guidelines. Clinical reports were issued to the ordering physician in accordance with CLIA/CAP regulations. Results: Of the 538 adults sequenced, 189 (35 %) had variants classified as pathogenic or likely pathogenic and expected to be clinically significant (heterozygous for a dominant condition, homozygous or compound heterozygous for a recessive condition). One hundred and five (20 %) had no pathogenic or likely pathogenic variants, but had a variant in a disease-associated gene classified as a suspicious variant of uncertain significance (VUS-S), which includes variants of uncertain significance in which there is suggestive evidence of disease causation. These VUS-S variants were found in a heterozygous state for a dominant condition and thus could be clinically significant. Regarding heterozygous carriers for recessive conditions, 471 (88 %) had variants classified as pathogenic or likely pathogenic and 36 (7 %) had VUS-S variants. Implications: Over one half of healthy individuals who underwent cWGS for the purpose of predisposition screening were found to have clinically significant variants with potential personal health implications. These data provide a general outline for what a predominantly healthy adult might expect from having a cWGS test based on the processes within ICSL, which may be useful in providing pre-test counseling for patients considering a cWGS test.

Germline Mosaicism Detection with Family-Centered Exome Sequencing: More Common than Previously Recognized?

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1. Ambry Genetics

When analyzing family histories, observing multiple similarly affected offspring without relevant family history is generally considered a strong indicator for autosomal and/or X-linked recessive disorders. Although germline mosaicism (GM) has significant implications for genetic counseling, statistics are limited and rates vary. Family-centered diagnostic exome sequencing (DES) is integral to enhanced diagnostic yield and discovering GM. Among a cohort of 510 consecutive unselected DES cases, we analyzed the diagnostic yield and origin of detected mutations in the first 50 families with healthy parents but at least two affected offspring. There was no difference (p=0.86) in diagnostic yields among the 50 cases when compared to the total cohort of remaining 460 cases (34.0 % and 35.2 %, respectively), indicating that the observation of multiple affected siblings is not a positive predictor for receiving a diagnosis. Among these 50 cases, 15 (24.0 %), were positive/likely positive for findings in characterized genes, 2 (4.0 %) with novel genetic etiologies, 3 (6.0 %) uncertain, and 30 (60 %) negative. Among the 15 positive/likely positive findings in characterized genes, 12 (66.7 %) are related to autosomal or X-linked recessive inheritance patterns, respectively. As expected, these two ratios (80.0 %) are significantly higher compared to the remaining 460 cases (31.6 %, $p< 0.001$). Perhaps the most interesting finding from this cohort was identification of autosomal dominant conditions arising from GM in 3 families: p.R257H in ACTG2, p.R209H in GNAO1, and p.E1799K in MTOR. These alterations were heterozygous in both the proband and an affected sibling, but absent in unaffected parents (reported biological relationships confirmed). The results of this study indicate that GM is seen in 6 % of DES families with multiple affected offspring and accounts for 20 % of positive finding, which is more common than previously documented. Discovering or ruling out GM has tremendous genetic counseling implications in regards to recurrence risk, family planning, and testing options.

Attitudes Toward Informed Consent Regarding Incidental Findings Among Parents of Children Undergoing Clinical Exome Sequencing

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Many laboratories currently offer whole exome sequencing (WES) as a diagnostic tool and its use will continue to increase as more diagnoses are made. Discussing the potential for discovering incidental (secondary) findings (IFs) during WES and the ability to opt out of receiving these findings are crucial parts of the informed consent process. Much research has focused on determining patient preferences for which IFs they would like the option of receiving. Additionally, many studies have evaluated provider experiences and attitudes toward informed consent and the return of IFs. The purpose of this study was to investigate parent attitudes toward informed consent regarding IFs and determine ways in which that process could be improved. Parents or guardians of children who underwent WES at the Kennedy Krieger Institute were invited to participate and 47 parents or guardians completed a survey that assessed their experience of providing informed consent for incidental findings in WES. All respondents recall having the informed consent discussion regarding WES, and the majority (61.5 %) reported the discussion was very helpful in aiding them in their decision whether or not to receive IFs. All respondents (n=12) who reported receiving IFs indicated they felt prepared to receive the results based on the informed consent discussion. Many respondents expressed their appreciation for the genetic counselor answering their questions and explaining WES. Some respondents commented on their gratitude for WES, but most of these individuals received a diagnosis from WES; others revealed their disappointment with WES and many of these individuals did not receive a diagnosis from WES. This study provides initial insight into patient perspectives of informed consent regarding incidental findings, but further study is warranted.

The Importance of Laboratory Genetic Counselor Review of BRCA Test Orders at LabCorp

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1. LabCorp

Genetic testing for inherited cancer can be complex and expensive. Genetic counselors play a critical role in proper test candidate identification and test selection. Unfortunately, not every medical center has access to a genetic counselor. For this reason, a laboratory genetic counselor can be a valuable asset when used to screen incoming test orders. At LabCorp, a genetic counselor reviews all BRCA test orders, clarifying comprehensive orders when a known familial variant is reported and targeted test orders when no variant information is provided. We reviewed 391 BRCA targeted analysis test orders received between December 2013 and February 2015. It was found that 153 (39 %) of these orders required updating when reviewed by a laboratory genetic counselor. While a negative familial variant result may warrant further testing by comprehensive analysis (depending on family history), a positive result would not. We found that 62 (40 %) of the orders updated from comprehensive to targeted were positive, representing a cost savings of around $148,490 by updating to targeted testing. In addition to financial benefit for the positive results, full gene sequencing can lead to finding variants of uncertain significance. More testing is not always better and could leave the patient feeling unsure about their risk even when negative for a familial pathogenic variant. Out of 238 BRCA samples ordered correctly, 112 (47 %) were through a clinical genetic counselor or nurse in genetics, while 126 (53 %) had no genetic counselor involvement prior to arrival at LabCorp. Therefore, combining the updated orders and those with no genetic counseling before arrival, 279 of the 391 (71 %) specimens in the study would benefit from laboratory genetic counselor review. This process could lead to significant healthcare savings and reduce unnecessary testing for patients who have not seen a genetic counselor, possibly reducing patient anxiety and uncertainty.

Marfan Syndrome or Not? An Unexpected Finding on Whole Exome Sequencing

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Patient AQ presented to our Genetics clinic at 2 years for evaluation of dysmorphic features, macrocephaly, developmental delay, anemia and subdural hematomas. There were no findings suggestive of a connective tissue disorder. Initial work-up was unrevealing. Whole exome sequencing (WES) was therefore obtained and did not identify a cause of this patient's phenotype. However, an incidental finding in the FBN1 gene [c.4270 C>G (P1424A)] was identified in this patient and his mother. This missense change has previously been reported in multiple patients with Marfan syndrome, and the reference laboratory classified it as a known pathogenic variant. *FBN1* testing of additional family members was pursued. AQ's brother and maternal aunt carry the same *FBN1* variant. Echocardiograms and ophthalmology exams were obtained on AQ, his brother, and his maternal aunt and were normal.

None of the family members with FBN1 mutations have any features of Marfan syndrome. While AQ and his brother are still young, AQ's 14 year old maternal aunt and 20 year old mother report no features of Marfan syndrome. Neither maternal grandparent reports any symptoms either. Furthermore, the P1424A change has an allele frequency of 0.0005 in 11,576 alleles from a Latino population sequenced in Exome Aggregation Consortium, and 0.0005 in 8,588 alleles sequenced in Caucasian Americans in Natinal Heart, Lund and Blood Insitute's GO Exome Sequencing Project. Given the lack of symptoms in this family and the allele

frequency in different populations, we question whether this variant really confers disease and this family really has Marfan syndrome or will develop symptoms in the future. With such ambiguity, the necessary course is screening the family as though they have Marfan syndrome. In the meantime we are increasing the family's stress and potentially ordering tests and spending additional health care dollars on screening that might not actually be necessary. This case illustrates the complexities and management challenges of WES and the presence of incidental findings in the absence of previous clinical suspicion.

Diversity Within: The Complexities of Genetic Heritage in the Latin American Population

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Introduction: The genetic pool is becoming increasingly homogenized and historically isolated cultures are now more genetically admixed. The Latin American population is one in which the complexities of genetic heritage are often overlooked. We aimed to understand these complexities by studying the predicted genetic ethnicity of individuals reporting Latin American ancestry and evaluating founder mutations identified in these individuals. Methods: Expanded carrier screening was performed for >1,500 subjects. Mutations with a >50 % detection rate were obtained, which typically imply a founder effect in 1 population and are thus less frequently expected in others. Patients identifying with 1 ethnic group were included. Carriers were identified for the founder mutations and categorized by reported ethnicity. Genetic ancestry was predicted by a statistical model based on 672 SNPs validated using the 1000 Genomes Project. Documented informed consent was obtained. Results: Individuals reporting Latin American ancestry were frequently identified as carriers of founder mutations associated with other populations. Mutations were associated with diseases such as ataxia telangiectasia, Bardet-Biedl syndrome, and Gaucher disease. Analysis of genetic ancestry demonstrated a high degree of genetic admixture within Latin American individuals. The 3 highest contributing ancestral groups were European (0.509±0.126), Native American (0.234±0.185), and African (0.101±0.183). Discussion: Results show that the Latin American population is genetically admixed, with a significant proportion of these patients identified as carriers for mutations associated with other ancestries. Findings highlight: 1) the disadvantages of conducting ethnicity-based carrier screening in populations with ethnic admixture, 2) the challenges of relying on patient-reported ancestries, and 3) the underestimation of reproductive risk for partners if carrier status is not identified. Thus, providing panethnic carrier screening for all patients is more clinically responsible, regardless of reported ethnicity.

Three Cases of Familial Pseudodominance in Pompe Disease: Are Current Practices Missing Diagnostic and Treatment Opportunities?

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Pompe disease (glycogen storage disease type II, acid maltase deficiency) has a broad spectrum of phenotype ranging from the classic infantile presentation with severe hypotonia and cardiomyopathy to a late onset form with a limb girdle muscular dystrophy and respiratory insufficiency. The U.S. Food and Drug Adminstration approved alglucosidase alfa enzyme replacement therapy (ERT) for Pompe disease in 2006. Clinical studies indicate that treatment with ERT results in improved clinical outcomes. We present three families with multigenerational, phenotypically variable Pompe disease. Case 1: In 2014 a proband presented with molecularly confirmed infantile Pompe disease. In 2015 her mother was molecularly confirmed to have late onset Pompe Disease (LOPD). Testing in the proband's full siblings determined that two, ages 4 and 6 years have LOPD. Case 2: A proband was enzymatically confirmed to have infantile onset Pompe in 1997. In 2008 her mother was molecularly confirmed to have LOPD. Case 3: In 1994 an adult sib-pair were enzymatically confirmed to have LOPD. In 2002 a first cousin twice removed presented with infantile disease. Molecular testing confirmed a common disease allele shared by these family members. Three additional cases of pseudo dominance in Pompe disease have been published previously – one parent–child pair and two grandparent-child pairs. In 2015, the United States Secretary of Health and Human Services added Pompe disease as a core condition to the Recommended Uniform Screening Panel for state newborn screening (NBS). Published data from NBS programs in Taiwan, Austria, and the state of Missouri, have all demonstrated a carrier frequency of Pompe disease higher than the previous estimate of 1/100. In a mixed U.S. based population, the carrier frequency for Pompe disease may be as high as 1/37. Careful consideration of family history or symptoms may warrant diagnostic evaluation for family members instead of targeted mutation testing.

Experience with Global Panethnic Genetic Carrier Screening in a Diverse Preconception Patient Population in Texas

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1. Progenity, Inc.

Current professional guidelines recommend offering carrier screening based on ethnicity, however a recently published joint commentary by genetic professionals and obstetricians noted the limitations of this strategy in an increasingly ethnically diverse population. Limited data has been published on the results of global carrier screening panels in multiethnic populations. We analyzed the results of a panethnic panel performed on an ethnically diverse patient population at a large reproductive medicine practice in Texas. Two hundred eighty-six preconception individuals underwent testing. The panel included testing for hemoglobinopathies, Fragile X (FX), and 20 disorders common in Ashkenazi Jewish populations (including cystic fibrosis (CF) and spinal muscular atrophy (SMA)). Testing included targeted mutation analysis for each condition, as well as hexosaminidase A (HexA) enzyme analysis, partial CBC, and hemoglobin fractionation. The majority (90 %) of the participants were female, with a high proportion of Hispanic individuals (36 %). Positive results were identified for 51 participants (18 %), with three individuals positive for two conditions. The most common positive result was the presence of an alpha-thalassemia deletion (12 patients - 6 of whom had normal MCVs and hemoglobin fractionations). Eight individuals were found to be carriers of Tay-Sachs disease, with the majority (75 %) identified as carriers through HexA analysis only. Thirty individuals were found to be carriers of SMA (9), CF (9), FX (8), or a variant hemoglobinopathy (4). Lastly, four patients were found to be carriers of the following disorders: Niemann-Pick disease (2), glycogen storage disease, and Gaucher disease. Results of this study suggest that global panels will likely identify carriers that may be missed through traditional ethnicity-based screening paradigms. Additionally, a dual method of carrier screening (i.e., DNA analysis in conjunction with enzyme or hemoglobin screening) for specific disorders increases the likelihood of identifying carriers.

Mosaic Tetrasomy 18p: Discordant Results Between Noninvasive Prenatal Screening and Fetal Karyotyping

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Abnormal results of noninvasive prenatal screening (NIPS) require confirmation by chorionic villus sampling or amniocentesis. We report an unusual cytogenetic disorder presenting as trisomy 18 by NIPS. The follow-up genetic amniocentesis for a 36-year-old woman showed two signals for chromosome 18 centromeric FISH probes. Because the signal for the centromere of chromosome 18 was polymorphic and therefore difficult to score in this patient's sample, additional FISH targeting 18q was performed. Two copies of 18q21 were observed by FISH. However, the final prenatal karyotype revealed an isochromosome 18p, tetrasomy 18p, in eight of fifteen colonies. Genetic counseling included a discussion about the likely *de novo* nature of the cytogenetic finding, but also noted recurrences of tetrasomy 18p reported in the literature. The variability associated with mosaicism was carefully reviewed as well as common characteristics such as developmental and cognitive delays. Parental karyotyping was offered and declined by the patient. The father was unavailable for testing. A second-trimester ultrasound and fetal echocardiogram were normal. The patient elected to continue the pregnancy to term and the baby was delivered at 39 weeks' gestation. The newborn had good tone and good suck reflex, was breastfeeding well, and was not dysmorphic. Karyotype in the newborn period confirmed mosaic tetrasomy 18p: 47,XY,+i(18) (p10) [3]/46,XY [42]. Discussion: This case illustrates the importance of fetal karyotyping in response to a positive NIPS result. Mosaic tetrasomy 18p was identified by prenatal karyotype analysis pursued in response to a positive NIPS for trisomy 18. This is a rare occurrence that adds to the literature regarding low-level mosaicism for tetrasomy 18p with an apparently normal phenotype at birth.

Analysis of Incidental Findings and Patient Preferences Regarding Return of Results in Medical Exome Sequencing

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As whole exome (WES) and whole genome sequencing are adopted as clinical diagnostic tools, identifying and reporting incidental findings is salient. The estimated chance of identifying a highly penetrant, pathogenic clinically actionable incidental finding is 1–5 % in individuals seeking WES. The purposes of this study were to elicit patient preferences regarding return of incidental findings and develop efficient methods for analyzing and identifying such findings in 41 patients with unexplained cerebellar ataxia undergoing partial medical exome sequencing. 26 patient samples were sequenced on an Illumina Hiseq 2500. Raw variants were filtered in Illumina VariantStudio to identify high-quality, rare, and functional variants in 3 curated lists of medically or reproductively significant genes. All candidate variants underwent manual review with data obtained from CLINVAR, HGMD, LOVD, and review of medical literature. Frequency of pathogenic variants from the list of 56 genes recommended by the American College of Medical Genetics was 3.8 % (n=1); frequency of carrier status for mutations in genes contained within Natera's Horizon Multi-Disease Carrier Screening panel was 19.2 % (n=5). Patient preferences regarding return of incidental findings were elicited via a consent form. Consistent with prior studies, nearly everyone (n=40) desired medically actionable incidental findings. The Fisher's exact test revealed patients' aged < 50 (n=15) were significantly more likely to prefer receipt of variants of uncertain clinical significance (p=0.023) and whole genome information (p=0.015) than those aged > 50 (n=26). This study is among the first to evaluate preferences regarding return of results in adults with neurologic disease. Moreover, scant published data exist regarding return of non-medically actionable incidental findings and variants of uncertain significance. Descriptions of the implementation of effective strategies for identifying and analyzing reportable incidental findings from whole exome sequencing in a research setting are provided.

De novo Pathogenic Variants in *DDX3X* are a Novel Cause of Intellectual Disability in Females

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Developmental delay and intellectual disability (ID) are heterogeneous disorders, and a genetic etiology is often not identifiable after standard karyotype, Fragile X, and microarray testing. Whole exome sequencing (WES) is an effective diagnostic tool, and it is especially powerful in identifying *de novo* variants using a trio approach that compares data from the affected proband and both parents. Through WES, we have identified 11 females from unrelated families who have novel predicted pathogenic heterozygous variants in *DDX3X*, a gene located on the X-chromosome. Ten variants were *de novo*, and parental samples were unavailable for the remaining case. *DDX3X* encodes a highly conserved DEAD-box RNA helicase that plays an important role in RNA metabolism; however, little is understood about human phenotypes associated with pathogenic variants in this gene. All 11 female patients (ages 1 to 18 years) harboring pathogenic *DDX3X* variants have ID ranging from mild to severe. Other common clinical features include hypotonia (10/11), structural brain abnormalities (8/11), dysmorphic features (8/11), behavioral problems (7/9), poor weight gain (7/11), abnormal sleep patterns (4/9), and microcephaly (4/11). Six patients had missense variants while 5 had variants that introduce a premature stop codon; however, there was no discernible difference in the nature or severity of their symptoms. Of 414 unique female probands with unexplained ID who underwent WES at our center, 2.9 % were found to have a predicted pathogenic variant in *DDX3X*. We describe a novel disorder characterized by ID and other variable neurological abnormalities in females, thereby providing a diagnosis and recurrence risk information for a large number of patients for whom a diagnosis has previously been elusive. Functional studies are

indicated to further determine the function of *DDX3X* on neural development.

Test Sequentially or Test Concurrently? An Analysis of Clinical Approaches to Expanded Carrier Screening

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Introduction: Patients are now increasingly offered carrier screening via expanded panels of over 100 diseases. Recent statements by professional societies provide guidance on how to approach the clinical use of such panels, including potential benefits of concurrent versus sequential screening for partners. Our aim was to understand approaches to expanded carrier screening in our population. Methods: Our initial analysis includes 64 patients referred for screening via an expanded panel. Patients received post-test genetic counseling; information regarding partner testing status and intention was gathered during the consults. Results: Of patients who had partners, 30 % underwent carrier screening concurrently and 70 % underwent screening sequentially. Among the patients who underwent screening sequentially, only 16 % of this group indicated that they would or were likely to pursue testing for the second partner, regardless of the first partner's carrier status. Discussion: Our analysis indicates the majority of couples undergoing expanded genetic carrier screening approach testing sequentially. While this may provide a cost savings, disadvantages include increased turnaround time and patient anxiety, particularly in the event of a positive screen during pregnancy. Results demonstrated the majority (84 %) of partners who approached screening sequentially were not planning to pursue testing for the second partner, regardless of carrier status. This presents a disadvantage as reproductive risks may be missed; additionally, the second partner is not able to learn meaningful information about their genetic health. Consideration should be given to recommendations regarding an appropriate approach to expanded carrier screening in order for couples to obtain the full benefits.

IX. Pediatrics

Whole Exome Sequencing Identifies *POGZ* Mutations as a Cause of Neurodevelopmental Disorders and Microcephaly

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De novo mutations play an important role in sporadic neurodevelopmental disorders due to the deleterious effect on reproductive fitness. For genetically heterogeneous disorders such as developmental delay and intellectual disability, whole exome sequencing (WES) can identify a genetic etiology in up to 30 % of cases when chromosomal array and fragile X testing are normal. WES testing using a trio approach that compares data from the affected proband and both parents can identify *de novo* variants in individuals with neurodevelopmental disorders. Of 2,415 patients referred for clinical WES for neurodevelopmental disorders, seven unrelated patients were found to have heterozygous changes that introduce premature stop codons in the POGZ gene, which we predict result in haploinsufficiency of the POGZ protein. Identified changes include nonsense and frameshift variants as well as one partial gene deletion. Six patients have *de novo* changes while the inheritance of the seventh patient could not be determined because parental samples were not available. All seven patients are developmentally delayed, and six patients whose cognitive status was known have intellectual disabilities. Four patients are microcephalic, with an additional patient having relative microcephaly. Additional features present in the majority of reported individuals include hypotonia, facial dysmorphism, and hands with broad and/or adducted thumbs and syndactyly. The POGZ gene is involved in normal kinetochore assembly and mitotic sister chromatid cohesion and mitotic chromosome segregation. The role of *POGZ* in mitosis suggests a possible role in regulating neuronal proliferation and could explain why patients with *POGZ* mutations are microcephalic and dysmorphic, including anomalies with craniofacial and limb development. WES is an effective diagnostic tool used to identify mutations among the large number of genes associated with neurodevelopmental disorders. Providing a molecular genetic diagnosis is important for accurate assessment of prognosis, risk of recurrence, and effective treatment options.

Investigation of Speech and Language Dsorders in Patients with 1p36 Deletion Syndrome

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Background: 1p36 deletion syndrome is a chromosomal terminal deletion syndrome, with an incidence ranging from 1/5,000–1/10,000. Speech impairment is considered to be almost universal among individuals with 1p36 deletion syndrome; however, there are no previous studies that clinically characterize the specific speech-language patterns and abilities within this population. The purpose of this study was to assess the communication abilities, as well as to describe the types of speech and language problems identified within this population. Methods: Formal speech-language evaluations were performed by certified speech-language pathologists on twenty-eight individuals (aged 1–17) with 1p36 deletion syndrome. Evaluations focused on assessment of the following domains: verbal ability, expressive language, and receptive language. Results: 54 % of participants (n=15) were verbal; specific verbal ability ranged from mildly to severely impaired. None of the participants were found to have age appropriate receptive or expressive language. 14 participants (50 %) showed signs characteristic of apraxia of speech. Of significance, only 5 of these individuals reported a previous clinical diagnosis of apraxia. Conclusions: Over half of our study population demonstrated verbal communication abilities, which directly contrasts with previous findings of absent expressive language in the majority of people with 1p36 deletion syndrome. In addition, our results illustrate a high prevalence of apraxia characteristics in the speech of individuals with 1p36 deletion syndrome. This information has the potential to impact the type of treatment recommended for these individuals as well as the counseling provided to families at the time of diagnosis. Further investigation into the specific speech and language skills of individuals with this deletion syndrome is warranted with a larger patient population.

Retrospective Study of Obesity in Children with Down Syndrome

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Background: Down syndrome is the most common live-born chromosome aneuploidy condition, and many features associated with this syndrome increase the risk for obesity. Few studies have conducted an in-depth review of children with Down syndrome with regard to obesity prevalence and health risk factors associated with obesity. Objectives: To characterize the obesity burden in children with Down syndrome by developing a trajectory of obesity throughout childhood and comparing the prevalence of obesity in our study population with the general pediatric population. We hypothesized that children with Down syndrome would have a higher prevalence of obesity, and those who are obese would have a higher co-occurrence of obstructive sleep apnea (OSA). Methods: This was a retrospective chart review that included children ages of 2 through 18 who have a diagnosis of Down syndrome. All children had been seen at Cincinnati Children's Hospital Medical Center with at least three height and weight measurements. The rate of obesity was compared to a local control cohort using contingency tables. Change in obesity rate through time was determined with mixed models. Impact of obesity on OSA risk was determined with contingency tables. Results: Of the 303 individuals evaluated, 47.8 % were obese (BMI>=95th percentile). This was significantly higher than the general pediatric population, of whom 12.1 % were obese ($p<0.0001$). BMI z-scores did not change markedly over time, indicating that those who were obese at young ages remained obese and those who were not obese at young ages remained non-obese. A majority of children with Down syndrome also had OSA, however, OSA risk was increased in obese children (RR=2.5, $p=0.0005$). Conclusions: Our data indicate that children with Down syndrome are at a substantial risk for obesity and OSA. These findings support the need for more aggressive weight management in early childhood and throughout the lifespan. Further studies of metabolism and growth are needed to determine the caloric requirements for children with Down syndrome.

The Path to Inclusion: Parent Perspectives on the Transition of Their Children with Down Syndrome into an Inclusion Classroom

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Many studies have been done on the benefits of inclusion for children with Down syndrome and their typically functioning classmates. The purpose of this study is to gain a greater understanding of the parent experience as their child transitions from Early Intervention or special education classes into an inclusion classroom. An online, anonymous survey was hosted by Qualtrics and distributed through the Massachusetts General Hospital and Boston Children's Hospital Down syndrome programs' Facebook groups. The survey contained multiple choice questions, Likert scale questions, and open-responses questions. We found that parents acted as advocates for their child in finding the people and resources that would best help their child be successful in the inclusion setting. Using chi square tests, we explored the relationship between birth order and perceived helpfulness of educational staff members and found no statistically significant differences between those who were the youngest or the middle child in their family and those who were the oldest or only child in their family. We also explored the relationship between income level and availability of resources and support and found no statistically significant differences between income levels. Every child with Down syndrome is unique and therefore their experiences with inclusion varied accordingly. However, parents' hopes for their child are the same as for any other child; they want them to be successful, have friendships, and become integral members of the school community. Genetic counselors need to make themselves aware of the issues faced by families who are raising children with Down syndrome. By understanding the challenges faced by families transitioning to an inclusion classroom, genetic counselors can align themselves with their patients and families to provide needed support.

Autism is not Always Present in Individuals with *ADNP* Mutations: Expanding the Helsmoortel-van der Aa Syndrome Phenotype

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Helsmoortel-van der Aa syndrome (HVDAS) (OMIM#615873) results from mutations in the ADNP gene and has recently been described as a cause of intellectual disability and syndromic autism. *ADNP* interacts directly with essential components of the BAF complexes, the functional eukaryotic equivalent of the SWI/SNF complex in yeast that is involved in gene expression. BAF complexes have critical functions in multiple aspects of neural development. Disorders caused by mutations in these complexes are sometimes referred to as SWI/SNF-related intellectual disability syndromes. To date, there have only been ten patients reported with HVDAS which limits the natural history and phenotypic information available. These ten patients were ascertained through a study looking at the prevalence of ADNP mutations in cohorts of patients with intellectual disability, autism spectrum disorder (ASD), and facial dysmorphisms. All ten patients had intellectual disability and ASD. Other features reported in these individuals with *ADNP* mutations include: short stature, obesity, congenital heart defects, feeding difficulties, joint laxity, small hands, hypotonia, seizures, and recurrent infections. Here we report on a 12-year-old male patient in whom whole exome sequencing revealed a *de novo ADNP* mutation. This same mutation was identified in two of the ten patients described by Helsmoortel et al. Our patient has several features in common with the ten patients, including: global developmental delay and intellectual disability, dysmorphic facial features, obesity, joint laxity, and hypotonia. Unlike the previously described patients, however, our patient does not have a diagnosis of ASD. Our patient also has several features not previously reported in individuals with *ADNP* mutations, including: strabismus, cryptorchidism, hidradenitis suppurativa, systolic hypertension, and hypothyroidism. Our patient is the eleventh patient described with an *ADNP* mutation. This case helps expand the phenotype associated with *ADNP* mutations and suggests that autism is not always present in these individuals.

Novel Discriminant Functions Based on Brain MRI Extra-Axial Fluid Measurements Allows Differentiation Between Glutaric Acidemia Type 1 and Benign Enlargement of the Subarachnoid Spaces of Infancy

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Glutaric acidemia, type 1 (GA1) can cause irreversible neurologic injury in an encephalopathic crisis. Early diagnosis and treatment have been shown to decrease morbidity and mortality by reducing the buildup of toxic metabolites. Characteristic findings on brain MRI can be seen in individuals that haven't had a crisis, which include enlargement of the perisylvian fissures, interhemispheric space, and spaces anterior to the temporal lobes. These spaces may also be increased in benign enlargement of the subarachnoid spaces of infancy (BESSI). Distinguishing

these diagnoses is critical, as failure to recognize and treat GA1 risks severe neurologic injury. A retrospective study of MRIs was performed for 3 groups: 10 individuals with GA1 and 30 age-matched individuals, 20 with normal brain MRIs and 10 with BESSI. Two raters measured seven extra-axial fluid spaces of each participant. These measurements were used to create three linear discriminant functions, which were able to discriminate among the three groups with reasonable accuracy. All control participants were classified correctly in the resubstitution and cross-validation studies. In the resubstitution analysis, 90 % of the BESSI and 80 % of GA1 groups were classified correctly; while 70 % of both the BESSI and GA1 groups were classified correctly in the cross-validation analysis. These results support the potential value of extra-axial fluid space measurements when considering GA1, though the functions should be validated in a larger cohort, as well as in low excretors and heterozygotes. Better distinction between individuals with GA1 and BESSI may help promptly identify affected individuals, while lessening unnecessary evaluation for GA1. This information may aid in genetic counseling for children whose genetic, enzymatic, and biochemical testing has not been diagnostic. Identification of characteristic MRI findings in an individual with a suspected diagnosis of GA1, while not diagnostic, may help providers and family recognize the ismportance of ongoing evaluation for an unconfirmed, but likely diagnosis.

Education of Children with Sanfilippo Syndrome: Identification of Needs, Challenges and Services Required for Children with Sanfilippo Syndrome by Their Parents

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Mucopolysaccharidosis type III (Sanfilippo syndrome) is a progressive, life-limiting, inherited metabolic disease characterized by severe behavioral manifestations and medical complications. Sanfilippo syndrome is often categorized into three stages of disease progression. The first stage is characterized by developmental delay, after a period of seemingly normal development. The second stage begins in early childhood and includes severe behavior problems and progressive mental deterioration. Specifically, children with Sanfilippo syndrome struggle with destructive, impulsive, and aggressive behaviors. The third stage is defined by motor deterioration and further neurological decline, ultimately leading to death. The behavioral manifestations and progressive nature of Sanfilippo syndrome are unique, thus traditional educational models for children with special needs may not be applicable. This study investigated the educational needs of children with Sanfilippo syndrome through parent interviews. Our results showed the difficulties parents of children with Sanfilippo syndrome face when choosing a school setting, and the need for an educational setting where the professionals have knowledge of the disease. The trajectory for developmental regression was also noted as a major challenge; however participants spoke of the positive impact of traditional services like physical, occupational, and speech therapy, as well as alternative therapies. Our results provide educators with a better understanding of the needs and services for children with Sanfilippo syndrome, as well as other children with behavior manifestations and developmental regression.

Adolescent-Centered Transition Program for Adolescents and Young Adults with Sickle Cell Disease

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Purpose: Pediatric genetic counselors often witness the difficult process families experience as their children age, and the challenges presented when navigating a new system of health care delivery. Young adults with sickle cell disease (SCD) are plagued with higher rates of morbidity and mortality than their pediatric counterparts. Our newly developed Adult Transition Program (ATP) at Howard University Center for Sickle Cell Disease (HUCSCD) provides a unique approach to this problem, as we are intimately familiar with the challenges new patients face when entering adult care. Methods: The ATP focuses on meeting the individual patient's and family's needs by assessing knowledge, willingness to transition, self-efficacy, psychosocial and executive performance, and presenting educational workshops throughout a year-long program. A case manager and patient navigator team enlist resources to manage multiple hospitalizations, social and psychological adjustments, and lifestyle behavior choices. Workshops provide education on managing healthcare and insurance, financial impacts, and genetics and reproductive issues. Exit interviews access changes in knowledge base, satisfaction, and willingness to transition. Results: To date, we have recruited 42 participants (48 % female) throughout the D.C. area. After year 1, analysis revealed that 74 % had at least one hospitalization per year, 38 % did not have a transition plan, and 42 % reported no discussion regarding adult care. In 22 followed-up participants, the following had improved from baseline to exit: knowledge (72 % vs. 100 %); readiness (32 % vs. 54 %); and efficacy (77 % vs. 79 %). Of note, parents' knowledge (5 % vs. 14 %) and readiness (5 % vs. 7 %) were poorer at baseline and exit, respectively. Conclusion: Our ATP is an effective model, providing education and empowerment to patients, while supporting for parents as they "let go" of their adult children. As a result, it ensures better health outcomes by facilitating a pathway to better healthcare management.

Online Cognitive Assessment of 15q11.2 Deletion Carriers Reveals Domain Specific Impairments

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Background: The 15q11.2 deletion has been implicated in a number of neurodevelopmental disorders, including developmental delay, schizophrenia, epilepsy, dyslexia, and dyscalculia. However, carriers with no associated phenotype have also been observed. The heterogeneity of presentation complicates genetic counseling and it can be difficult to interpret findings of 15q11.2 deletion for patients and families. Finding and categorizing a possible intermediate or associated phenotype in 15q11.2 deletion carriers would provide important insight into the neurobiology associated with the deletion, and aid clinicians in the challenging task of providing patients and families with a clearer understanding of the potential range of outcomes. Methods: To investigate cognitive function in 15q11.2 deletion carriers, we used an online platform called Lumosity, which employs well-established neuropsychology tests to look at cognitive functions including memory, speed, attention, flexibility, problem solving, and logical reasoning. A cohort of 27 15q11.2 deletion carriers participated in a series of internet-based video games designed by Lumosity. We matched each deletion carrier with 100 controls based on gender, age, and level of education. Controls were assumed to not carry the 15q11.2 deletion, which has a population prevalence of 1/500. Results of their tests were obtained from Lumosity. Results: We compared each subject's score to a mean score for the cohort of 100 matched controls. Subjects were compared to controls for 10 different tasks. Although on average deletion carriers scored lower and performed slower in all the tasks, the results were significant for Grammatical Reasoning and Wordy Equation tasks, with P values of 0.00187 and 0.00144 respectively. Discussion: Results suggest that individuals with 15q11.2 deletion who

function within the norm in the general population, perform significantly worse than the general population in tasks that involve arithmetic problem solving and logical reasoning, providing evidence for the presence of an intermediate phenotype.

Two Siblings with a New Form of Spondyloepimetaphyseal Dysplasia: No Closer to a Diagnosis After Negative Whole Exome Sequencing

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Spondyloepimetaphyseal dysplasias (SEMD) are a heterogeneous group of disorders characterized by radiographic abnormalities of the spine, epiphyses and metaphyses of the long bones. There are currently 13 described OMIM types with 7 known genes. Here we present siblings with an unknown type of SEMD for whom whole exome sequencing (WES) has been uninformative. Proband 1 is a term male African American born after a pregnancy complicated by polyhydramnios and poor fetal growth. Prenatal U/S demonstrated spinal curvature, rhizomelia, and a small bell-shaped thorax. Amniocentesis revealed a normal 46, XY karyotype. Skeletal surveys performed both at 2 days and at 8 months of age showed a hypoplastic maxilla, increased mandibular angle, hypertelorism, thoracolumbar kyphosis with wedged and beaked L1, and flattened acetabular angles with a champagne-glass configuration of the bony pelvis. The metaphyses were broad and smooth with small epiphyses. All metacarpal and metatarsal bones and phalanges were short and thick. Expert review of the films confirmed SEMD, unclassified type. Labs revealed normal urine oligosaccharides and glycan screening, a single nucleotide polymorphism (SNP) microarray with multiple inherited copy number variants (CNV) of unknown significance and normal blood *FGFR3* and *TRPV4* sequencing. Proband 2 is the female sibling to proband 1, born at 36-2/7 weeks gestation. The pregnancy was complicated by poor fetal growth and shortened long bones. Skeletal surveys performed after birth showed dolichocephaly, multiple vertebral bodies with beaking and other similar findings to her brother. A SNP microarray revealed the previously detected inherited CNVs of unknown significance. WES was sent and found no clinically relevant changes. As the children carry multiple inherited CNVs; these are unlikely to contribute to the phenotype. We hypothesize there is a mutation in an unidentified gene, either inherited autosomal recessively or a germline mutation, responsible for the children's phenotype.

Carey-Fineman-Ziter Syndrome can be Caused by Mutations in *TUBB3*

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Carey-Fineman-Ziter Syndrome (CFZS; OMIM# 254940) is a disorder characterized by a congenital, non-progressive myopathy combined with Moebius Sequence, Pierre-Robin sequence, and growth delay. The first case was described by Carey et al. in 1982 in a brother and sister with these features. Since that time twelve cases of suspected or diagnosed CFZS have been reported. To date, no genetic etiology has been identified. We report a case of CFZ syndrome in a 5 year old who was found to have a likely causative mutation upon whole exome sequencing (WES). At birth (36 weeks gestation), patient was noted to have micrognathia with cleft palate, frontal bossing with sunken eyes and cortical thumbs. Newborn complications included respiratory distress and stridor secondary to true vocal cord paralysis. He also had facial nerve palsy and subsequent feeding difficulties, which necessitated gastrostomy tube placement. Initial diagnoses were Moebius and Pierre-Robin sequences, although his symptoms went beyond the Moebius-Robin spectrum. Gross motor delays in the first year prompted a diagnosis of hypotonia. EMG and muscle biopsy results suggested congenital, non-progressive neurogenic myopathy. His features in conjunction with his myopathy were felt to be consistent with Carey-Fineman-Ziter Syndrome. WES identified a *de novo* missense mutation in exon 4 of *TUBB3*, mutations in which have previously been described as causative for congenital fibrosis of the extraocular muscles type 3 (CFEOM3). *TUBB3* plays a major role in axonal migration and microtubule stability, which could explain the features of Moebius and Pierre-Robin sequences as well as the myopathy in Carey-Fineman-Ziter Syndrome. Based on these findings, we suggest that Carey-Fineman-Ziter syndrome is allelic to CFEOM3 and feel that additional testing of known CFZS patients for *TUBB3* mutations is warranted. Additionally, for at least a subset of CFZS patients, the inheritance pattern may actually be a new dominant disorder as opposed to an autosomal recessive condition.

Parents' Information-Seeking Journeys Related to Their Child's Rare Disorder: A Qualitative Study

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Background: Previous research demonstrates that parents of children with chronic health conditions are dissatisfied with the quality and quantity of information received from healthcare providers (HCPs), as well as the manner of delivery. However, the majority of parental health information-seeking studies center on relatively common chronic childhood conditions, such as cancer, kidney disease, and congenital heart defects. Therefore, parents of children with rare disorders face greater challenges acquiring information related to their child's disorder because of the limited knowledge about rare conditions. The purpose of this study is to explore parents' journey in seeking information related to their child's rare disorder, and document their recommendations to HCPs and similar parents. Methods: We use a qualitative methodology utilizing data from interviews and focus groups, analyzed in a thematic framework. Here, participants consist of parents or primary caregivers of an individual with a rare genetic disorder. Results: Parents face difficulty gathering information from HCPs and the healthcare system, motivating them to seek information on their own. This process often forces parents to become experts of their child's condition, as well as educators of their child's HCPs. Parents recommend that HCPs provide more resources when first disclosing their child's condition, and help disseminate the knowledge parents accumulate during their information-seeking journey. Our participants advise rare-disorder parents to become informed, share their knowledge with HCPs, and interact with other affected families. Conclusion: A parent's information-seeking process goes beyond just wanting more information from HCPs: parents want to be incorporated into the process of creating and disseminating information. HCPs can learn from the wealth of knowledge that parents accumulate on their journey, partnering with them to share this information and improve their healthcare experience.

Exome Sequencing Identifies a Rare Case of Birk-Barel Syndrome Caused by a Mutation in the Paternally Imprinted KCNK9 Gene

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Introduction: Birk-Barel mental retardation dysmorphism syndrome is characterized by moderate to severe mental retardation, hypotonia, cleft palate, micrognathia, dysphagia and reduced facial movement. Dysmorphic features include a narrow, elongated face and flared, bushy eyebrows. The syndrome is caused by a pathogenic variant in the KCNK9 gene, located at 8q24.3. The gene falls within an imprinted region resulting in expression of the maternal allele and silencing of the paternal allele. Case Report: We report on a male evaluated by genetics in the neonatal period due to cleft palate, micrognathia, hypotonia, leg length discrepancy and phymosis. A diagnosis of Prader-Willi syndrome (PWS) was considered, however both a genome wide single nucleotide polymorphism (SNP) array and methylation analysis of the PWS critical region were normal. The proband was evaluated in genetics clinic for a follow-up appointment at 7 months of age. A hypotonic face with a thin upper lip, reverse cupids bow of the lower lip, thick gums, and retrognathia was noted. Exome sequencing of the proband and both parents was pursued through our laboratory. We identified a *de novo* pathogenic variant within *KCNK9* that had been previously described in the first and only case report on Birk-Barel syndrome. Proximity with an inherited polymorphism allowed us to determine phase by examining the next generation sequencing reads from the proband and each parent. The *de novo* pathogenic variant was in *cis* with a polymorphism inherited from the mother, thus proving a diagnosis of Birk-Barel syndrome. The diagnosis led to the discovery of other affected families via social media, as well as information regarding potential drug therapies. Discussion: Birk-Barel syndrome is a rare genetic form of intellectual disability due to maternally inherited pathogenic variants in the KCNK9 gene. Exome sequencing led to a diagnosis of Birk-Barel syndrome, which affected medical management and recurrence risk counseling for the proband and his family.

CHOPS Syndrome: A Novel Genetic Diagnosis Characterized by Cognitive Impairment and Coarse Facial Features, Heart Defects, Obesity, Pulmonary Involvement, Short Stature and Skeletal Dysplasia

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Three unrelated probands have been followed in the Center for Cornelia de Lange syndrome and Related Diagnoses at The Children's Hospital of Philadelphia (CHOP) for a combined 12-year period who were all initially referred due to a suspected diagnosis of Cornelia de Lange syndrome (CdLS). All three probands had features overlapping those seen in CdLS including developmental and speech delays, intellectual disability, and short stature with small hands and feet. However, all three probands had several distinct features not associated with CdLS including obesity, vertebral anomalies, bracydactyly and respiratory findings such as laryngomalacia, tracheostomy and chronic lung disease making a diagnosis of CdLS unlikely. Additionally, though they had dysmorphic features including synophrys and arched eyebrows (which is seen in CdLS), they had distinct coarse facies with a round face which is not typically observed in CdLS. Extensive testing throughout the course of their care was negative including screening by single nucleotide polymorphisms (SNP) array, multi-gene panel analyses, and biochemical disorder screening including mucopolysaccharadisoses. The underlying genetic etiology remained unknown until exome sequencing through research efforts at CHOP identified a *de novo* missense mutation in the AFF4 gene in all three probands. *AFF4* plays an important role in regulating transcriptional elongation which is a critical mechanism by which gene expression is regulated during development. Somatic mutations in genes that control transcriptional elongation have been previously described in cancers but to our knowledge this is the first human developmental disorder caused by a germline mutation. Developmental diagnoses caused by disruption of normal transcriptional processes are collectively termed "transcriptomopathies". This new diagnosis has been named CHOPS syndrome (C for Cognitive impairment and Coarse facies, H for Heart defects, O for Obesity, P for Pulmonary involvement and S for Short stature and Skeletal dysplasia). The clinical features and natural history of CHOPS syndrome will be presented.

Investigation into Inherited Metabolic Disease Clinic Practices for Follow Up of Positive Very Long Chain acyl-CoA Dehydrogenase Deficiency Newborn Screen Results

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Background: Very long chain acyl-CoA dehydrogenase deficiency (VLCADD) is a fatty acid oxidation disorder included on every state newborn screen (NBS). Age of onset and severity are variable and penetrance is incomplete. Symptoms include hypoglycemia, lethargy, muscle weakness, liver abnormalities, and life-threatening heart problems. Triggers include periods of fasting, illness, and exercise. Diagnosis relies on documenting a substantial reduction in VLCAD enzyme activity or presence of two pathogenic mutations in the ACADVL gene. In some cases, biochemical and genetic results make it difficult to distinguish affected from unaffected individuals, impacting management and genetic counseling for these families. The purpose of this study was to ascertain how metabolic physicians diagnose and follow children with an unclear VLCADD diagnosis. Methods: Study subjects were recruited through Metab-l listserv via an email which contained a description of the study and a link to an anonymous survey. Statistical analyses were performed to evaluate differences in responses based on geographic location and number of years of newborn screen follow-up experience. Results: A total of 19 individuals participated. There was no consistent follow-up protocol among metabolic physicians for a child positive for VLCADD on newborn screen. No differences in responses were observed based on geographical area of practice (U.S. versus non-U.S.) or provider experience. More than half of the respondents indicated that they perform literature review for updates in classification of reported variants of uncertain significance. Discussion: This exploratory study found that variability exists in metabolic physicians' clinical approach to a newborn with an unclear diagnosis of VLCADD. The reasons for this variability are unknown. It is important for genetic counselors to be familiar with the variability in VLCADD presentation and medical management approach in order to help families understand and cope with the uncertainty of the diagnosis.

The Myelin Disorders Bioregistry Project: A Bioregistry for Patients with Known and Unsolved Genetic Disorders of the White Matter

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Introduction: Leukodystrophies are a heterogeneous group of heritable disorders characterized by abnormal signal of the white matter on brain magnetic resonance imaging (MRI). Common clinical symptoms include delayed milestones, spasticity, dystonia, and ocular movement abnormalities. Pattern recognition on MRI can aid in reaching a diagnosis; however, historically nearly 50 % of cases remain unsolved. We ascertained the current rate of molecularly confirmed leukodystrophies within a

research cohort. Purpose: The Myelin Disorders Bioregistry Project (-MDBP) is a bioregistry that aims to develop diagnostic and therapeutic approaches for leukodystrophies and provide support opportunities for families living with these rare conditions. Methods: Families and/or physicians reach out to the MDBP team for inclusion. Medical records and blood samples are collected. Patients with known leukodystrophies are included for future studies on therapeutics of the disorder and patients with an unknown genetic diagnosis may undergo next generation sequencing (NGS) technologies to identify known and novel conditions. Results: The MDBP has enrolled 569 participants. Participants without a complete file were excluded from analysis (n=104) for a total of 465 active cases. 150 families were unsolved from this group (32 %). Of those 150, 22 % (n=34) underwent NGS but no known or likely pathogenic variants were identified. New disease entities have been described and known disorders have been clinically expanded. Four family conferences have allowed families to connect and further characterize these disorders. One clinical drug trial is currently under review. A diagnosis was achieved or known in 76 % of cases over 10 years of recruitment. Conclusions: The MDBP hosts a group of genetically diverse leukodystrophy patients. MRI pattern recognition and NGS technologies may provide an effective methodology for diagnosis in the leukodystrophies, with a predicted decrease of unresolved cases to 20 %. A specific diagnosis may decrease the disease burden of an unsolved leukodystrophy by permitting targeted disease management and support.

Pilot Study of Attention Deficit Hyperactivity Disorder-Related Behaviors in a Pediatric Ehlers-Danlos Syndrome-Hypermobility Type Population

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Introduction: Clinical observation in the Cincinnati Children's Hospital Medical Center (CCHMC) Connective Tissue Clinic (CTC) as well as recently published research suggests a link between joint hypermobility and attention deficit hyperactivity disorder (ADHD). However, existing studies are few in number and of limited clinical utility. The primary goal of this pilot study was to examine the relationship between Ehlers-Danlos syndrome-Hypermobility type (EDS-HT) and attention-related behaviors in order to assess whether further studies might be warranted. Methods: The parents of 12 children with EDS-HT seen in the CCHMC CTC (cases) and 7 non-hypermobile children (controls) seen in a local pediatric office completed the Child Behavior Checklist (CBCL) to rate the participants on a variety of behaviors. The CBCL contains multiple scales, of which we examined sixteen. Comparisons of t-scores for each CBCL scale were performed using Wilcoxon rank-sum test. T-scores were also dichotomized and proportions of borderline/clinical range scores (t-score >= 65) were compared between cases and controls using Fisher's exact test. Results: Compared with controls, cases showed significantly higher t-scores on the Sluggish Cognitive Tempo (SCT) scale (p=0.006). Scores on the SCT scale correlated highly with scores on the Attention Problems syndrome scale (R=0.83) and ADHD Problems DSM-oriented scale (R=0.70). When scores were dichotomized, the two attention-related CBCL scales were among the scales that showed the largest difference in proportion of cases with t-scores >= 65 (ADHD Problems DSM-oriented scale, p=0.147).

A Patient with *PTEN*-Associated Macrocephaly and Autism Presenting with Thyroid Follicular Adenomas (Cowden Syndrome)

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Patient was evaluated by a pediatric neurologist at 15 years of age following a single seizure in presence of an afebrile illness. She had a history of macrocephaly with an arachnoid cyst and pervasive developmental disorder diagnosed in the first few years of life. Given her history, diagnostic studies were obtained and included urine organic acid analysis, plasma lactate, Fragile X testing and array comparative genomic hybridization (aCGH), all of which were normal. Plasma amino acids were also obtained, and revealed elevated plasma free-homocystine, undetectable cystathionine, and normal methionine. She was therefore referred to Genetics for evaluation of elevated homocystine. She subsequently had an extensive evaluation for persistent hyperhomocystinemia which was unrevealing.

At 19 years of age, she developed hyperthyroidism and underwent thyroidectomy. Thyroid tissue pathology revealed multiple follicular adenomas, suggestive of Cowden syndrome. *PTEN* sequencing was performed and revealed a previously reported pathogenic mutation (c.407 G>A; C136Y). This finding also explains her history of macrocephaly and pervasive developmental disorder. Parents were tested and the mutation was not identified in either parent. Current recommendations call for PTEN testing in the presence of macrocephaly and autism, even in the absence of other features. This patient presented in her first years of life with autism spectrum disorder and macrocephaly. She was born before macrocephaly and autism were known to be associated with *PTEN* mutations, and she was only diagnosed with a *PTEN* mutation after findings of follicular adenomas on resected thyroid tissue. This case highlights the increased risk of cancer in patients with *PTEN* mutations who originally present with only macrocephaly and autism spectrum disorder, and confirms the need for cancer screening in those patients, even while still teenagers.

A Model for a Multidisciplinary Epilepsy Genetics Program

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It is estimated that 3 million Americans and 65 million people worldwide live with epilepsy, a condition characterized by recurrent unprovoked seizures that leads to significant morbidity and mortality. Epilepsy may be caused by a variety of factors, and increasingly genetic factors have been recognized as a major contributor. Since the first epilepsy gene was identified in 1994, there have been dozens of novel epilepsy gene discoveries, particularly among patients with early onset, intractable epilepsy accompanied by neurodevelopmental disability. There are already several examples of treatment recommendations that can be made based on molecular diagnoses, and small-scale precision-treatment trials are underway The Epilepsy Genetics Program (EGP) at Boston Children's Hospital, founded in 2011, is the first multidisciplinary program that provides clinical consultation to families of children with known or suspected genetic epilepsy syndromes, as well as conducting translational research to advance genetic knowledge and treatment outcomes. The Program is staffed by 2 pediatric epileptologists and 2 licensed genetic counselors as well as several laboratory researchers. Our weekly clinical service is devoted to addressing diagnostic, genetic counseling and treatment related issues. Patients with known molecular diagnoses have the option of participating in gene-specific protocols such as the *PDH19*-Related Epilepsy Patient Registry. For patients in whom currently available clinical testing yields no diagnosis, the Program offers enrollment into research protocols that incorporate expert review of variant pathogenicity, such as the Epilepsy Genetics Initiative. Finally, the EGP's laboratory facilities and collaborations enable functional assessment of epilepsy gene variants using animal models and pluripotent stem cell protocols to assess both variant pathogenicity and drug response. Ultimately the findings from these approaches will lead to additional precision-treatment clinical trials for patients with epilepsy.

Genotype-Phenotype Correlation for NF1A Gene as Part of Microdeletion 1p32.1p31.3 Syndrome

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The NFI family of genes encodes transcription and replication proteins in adenovirus and eukaryotic cells *in vitro*. In vivo studies on homozygous Nfia −/− and heterozygous Nfia +/− mice show that a lack of gene product is associated with hydrocephalus, agenesis of the corpus callosum and urinary tract defects. The 1p32p31 microdeletion syndrome in humans (OMIM #613735), which encompass the NFIA gene (OMIM 600727), has been associated with similar central nervous system malformations as well as macrocephaly, developmental delay and dysmorphic features, in conjunction with urinary tract abnormalities. To date, only seven patients with 1p32p31 microdeletion syndrome, along with two patients with translocation-mediated disruption of the NF1A gene, have been reported. We report a case of a *de novo* 1.936Mb deletion of chromosome 1p32.1p31.3 which includes the NFIA gene and two other genes *TM2D1* and *INADL*. The patient is a 9 year-old boy who, to date, does not have developmental delay despite central nervous system malformation in the form of dysgenesis of the corpus callosum and ventriculomegaly. He is also non-dysmorphic and does not have urinary tract malformations. Furthermore, unlike the previously described patients he has the unique features of hyperopia, esotropia and amblyopia in the left eye. While it is not clear whether his ocular findings are directly associated with the microdeletion per se, the absence of developmental delay, dysmorphic features and urinary tract malformation argue that haplo-insufficiency of the NF1A gene is necessary, but not sufficient, in itself, to cause cognitive impairment, craniofacial dysmorphism and urinary tract defects. Other modifier gene(s) and environmental factors may also play a role in phenotypic outcome.

Review of 33 Cases of Clitoromegaly: Causes and Outcomes

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Newborns presenting with ambiguous genitalia can lead to counseling sessions that often include uncertainty about the prognosis of the child. We conducted a retrospective chart review of newborn patients seen at Greater Baltimore Medical Center presenting with enlarged clitoris over the past 25 years. There were a total of 33 females with clitoromegaly. For members of our cohort who had hormonal studies, 24 % had elevated testosterone and 18 % elevated 17-OH-progesterone. In addition, 9 % of mothers had self-reported a larger than average clitoral size, and 6 % of sisters and/or aunts, for 15 % with a maternal family history. Notably, 12 % of the newborns were the result of an *in vitro* fertilization (IVF) pregnancy and 24 % were exposed to progesterone, both of which are elevated over population rates. All patients had normal XX chromosomes. There was variability in outcomes and identified etiologies. Twenty six (79 %) had a spontaneous resolution of the enlarged clitoris and seven (21 %) had continued growth. Three (10 %) were found to have a known genetic condition – two had 21-hydroxylase deficiency (CAH) and one had Beckwith-Weidemann syndrome. An additional four were identified as having an unknown genetic disorder. Additionally, five (13 %) of the patients had developmental delay. While endocrine disorders such as CAH are reported in the literature as the most frequent cause of enlarged clitoris, it was the etiology for only two (6 %) members of our cohort. These data illustrate that there are multiple etiologies and that clitoromegaly may resolve over time. Our findings can be used to shape medical management and counseling of families with newborn presenting with clitoromegaly. For parents of newborns our data introduce more ambiguity into early diagnoses but also provide more hope for resolution without apparent consequence. Future research may explore larger cohorts and longer-term outcomes of newborns with this malformation and the potential relationship with IVF pregnancies.

Twenty-Year Follow-Up of Newborn Screening for Patients with Muscular Dystrophy

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Introduction: Consideration of including muscular dystrophy in newborn screening (NBS) panels is highly relevant to the families affected by muscular dystrophy and their physicians. A unique population of young men entering adulthood who received a diagnosis of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD) during a pilot NBS program in Pittsburgh, Pennsylvania from 1987 to 1995 provides an exceptional opportunity to obtain insight into the patient and family experience with NBS for these disorders and resulting attitudes towards NBS. Methods: To assess these experiences with and attitudes towards NBS, we surveyed families with sons affected by DMD or BMD and born during the pilot NBS program, stratifying into 2 groups: those identified by NBS (sons n=8; parents: n=10) and those identified by the traditional diagnostic process that generally occurs after symptom onset (sons: n=7; parents: n=15). Results: All parents in the NBS cohort and 14 of 15 (93.3 %) parents in the non-NBS cohort supported NBS for DMD and BMD. All NBS and non-NBS patients supported NBS for DMD and BMD. The non-NBS parent cohort felt that NBS would cause increased anxiety; however, this was not a concern in the NBS parent cohort. Discussion: There was strong support for NBS for DMD and BMD in both groups of patients and parents regardless of whether diagnosis was by NBS or after symptom onset. Parents who received the diagnosis of DMD or BMD for their son by NBS indicated a preference for this means of early diagnosis even in the absence of available pre-symptomatic treatment.

Very Small Familial Microdeletion of 15q11.2 Results in an Atypical Prader-Willi Syndrome Phenotype

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We present a family with atypical Prader Willi Syndrome (PWS) caused by an unusually small 106 Kb deletion of 15q11.2. Initial testing found the typical abnormal PWS methylation pattern in the absence of a detectable deletion by FISH. Subsequent microarray verified a deletion that includes only a portion of the 3' end of the SNRPN gene and the 5' end of the snoRNA gene cluster, proximal to *SNORD116*. Our family includes at least two affected full siblings, one male, one female, ages 15 and 13, respectively. They meet clinical criteria for PWS, but their phenotype is mild and some facial and neurologic features are unique to the sib pair. Only the brother had early feeding issues with relatively late onset of mild

hyperphagia. The sister never had early feeding problems, but had poor weight gain in early childhood. Now, weights are normal for age, but increased for height, with hyperphagia relatively well-controlled. Both have short stature and hypogonadism, obstructive sleep apnea, small hands and feet, mild intellectual disability, and behavior problems. The sister has cataplexy, and now has developed intention tremor and dysmetria of as yet uncertain etiology. Although common paternity was initially denied, chromosome microarray confirmed that both siblings and their father carry the familial deletion. This family further refines the critical region for the PWS phenotype and illustrates that very small, paternally-inherited 15q11.2 deletions may be associated with a more limited, atypical form of PWS.

Anxiety in Adolescents with Neurofibromatosis Type 1

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Neurofibromatosis type 1 (NF1) is a common genetic condition characterized by both physical (café-au-lait spots, neurofibromas, skeletal abnormalities) and neurodevelopmental manifestations (learning disabilities and attention deficit disorders). During adolescence, both aspects of the condition may become more evident to affected individuals as well as their peers. In the general population, approximately 8 % of adolescents have anxiety and fewer than 20 % of these individuals receive care for the disorder. We hypothesize that anxiety is more common in adolescents with NF1 and that they are more likely to experience anxiety than their unaffected siblings. We invited adolescents with NF1 and their unaffected siblings to participate in an online survey. Participants were either members of the Utah Chapter of the Children's Tumor Foundation or the NF Registry. This survey assessed manifestations of NF1, family history of the condition, co-morbid conditions, school performance, use of medications, and the possibility of anxiety based on assessment by the Screen for Anxiety Related Disorders (SCARED) assessment. Analysis included 38 adolescents from the Utah Chapter of the Children's Tumor Foundation and 10 adolescents from the NF Registry. Overall, 38 (78 %) adolescents had NF1 and 11 (22 %) adolescents were unaffected siblings. Our results indicate no statistically significant correlation between anxiety and NF1 status; however, 40 % of the affected survey respondents indicated significant predictors of anxiety on the SCARED assessment (five times greater than the average rate reported in adolescents). We identified a statistically significant correlation between rarer manifestations of NF1 (plexiform neurofibromas, tibial bowing, and scoliosis) and higher levels of anxiety in affected study participants. Self-reported below-average performance in language arts positively correlated with anxiety as was use of anxiety/depression medication. As part of anticipatory guidance in NF Clinics, discussion of potential anxiety risks for adolescents is appropriate.

Mutations in *ARID2* are Associated with Syndromic Intellectual Disabilities

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The etiology of syndromic intellectual disabilities (ID) remains unknown for the majority of patients. Due to reduced reproductive fitness in many individuals with ID, *de novo* mutations account for a significant portion of severe ID. In this study, we used clinical whole exome sequencing (WES) in proband-parent-trios to identify the etiology of syndromic ID. We identified four independent, novel, loss of function variants in the ARID2 gene in four patients, three of which were confirmed to be *de novo*. *ARID2* is an intrinsic component of Polybromo-associated BAF (PBAF), which is part of the SWI/SNF subcomplex. The ATP-dependent SWI/SNF chromatin modifier has previously been linked with neurodevelopmental disorders including ID and autism. All four novel variants are predicted to lead to a premature termination with the loss of the two conservative zinc finger motifs. The patients all have ID and share other clinical characteristics including attention deficit hyperactivity disorder, short stature, Wormian bones and dysmorphic facial features such as plagiocephaly, retrognathia, micrognathia and low set, posteriorly rotated ears. Other features found in some but not all affected individuals include macrocephaly, highly arched palate, and cleft palate associated with Pierre Robin sequence. This is the first report of mutations in *ARID2* associated with developmental delay and syndromic ID. In the quest to provide a molecular genetic diagnosis for heterogeneous disorders such as syndromic ID, whole exome sequencing (WES) is an effective diagnostic tool for exploring the genetic etiology of these disorders and offers an opportunity to provide families with a prognosis, risk of recurrence, and potentially, a network of other families with similarly affected members.

Two Cases of 2p16.3 Microdeletion Including *MSH6* and *FBXO11*: Are Developmental Delays and Other Clinical Features Related?

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Chromosomal microarray analyses revealed 2p16.3 microdeletions including the MSH6 and FBXO11 genes in two unrelated children. *MSH6* haploinsufficiency causes Lynch syndrome, an adult onset hereditary cancer syndrome. *FBXO11* is associated with ubiquination and transforming growth factor β signaling, but the clinical phenotype of germline haploinsufficiency is currently unknown. Both children were referred for cancer genetic counseling based on the *MSH6* deletion. One is a 12-year-old male who was born at 34 weeks' gestation and had respiratory failure in the neonatal period. He has tracheo-esophageal fistula, chronic lung disease, developmental delay, and seizures. Oligo microarray detected a 0.5 Mb loss (hg18 coordinates: 47,381,791–47,887,705) later found to be maternally inherited. The family did not pursue recommended cancer genetic counseling until after his mother was diagnosed with stage IV colorectal cancer at 48 years of age. Family history is also significant for esophageal cancer diagnosed in a maternal uncle at age 40. The second child is a 4-year-old male with developmental delay and dysmorphic facial features. He was born at 39 weeks' gestation and was admitted to the NICU for feeding and breathing support for 3 weeks. He also has truncal hypotonia. Audiology evaluation due to expressive language delay showed moderate unilateral conductive hearing loss, and he required placement of typanostomy tubes. Single nucleotide polymorphism microarray showed 0.18 Mb loss (hg18 coordinates: 47,884,950-

48,060,992) later found to be maternally inherited. Family history is significant for mild intellectual disability in his sister and mother. In both cases, results from other genetic and biochemical tests have been non-diagnostic. Ethical considerations must be considered in that these analyses identified an adult onset condition in the pediatric population. Additionally, the association of intellectual disability with similar small deletions in two families may implicate the contiguous genes *MSH6* and *FBXO11* in patients with both Lynch syndrome and intellectual disability.

X. Pre- and Perinatal

Diagnosis of an Unbalanced Fetal Translocation Following Abnormal Cell-Free DNA Screening

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Introduction: Noninvasive prenatal screening (NIPS) analyzes circulating cell-free (ccf) fetal DNA derived from maternal plasma for common fetal aneuploidies. This testing was originally validated for the identification of trisomies 13, 18 and 21; however, massively parallel shotgun sequencing (MPSS) analysis of ccf DNA looks for over- or under-representation of genomic material, and therefore has the potential to identify smaller copy number variants as well. We present a case of abnormal cfDNA screening results leading to the diagnosis of an unbalanced fetal translocation. Case Report: A 29-year-old woman was referred to specialist care following the identification of a suspected fetal brain anomaly on ultrasound. After genetic counseling and maternal-fetal medicine evaluation, the patient elected cfDNA screening. Abnormal results revealed an underrepresentation of chromosome 18, suspicious for either partial or full monosomy 18. Karyotyping of amniocytes revealed an abnormal karyotype consistent with a deletion of chromosome 18 (46,XY,del (18) (q21.3)). Results of microarray analysis revealed an apparently unbalanced translocation, consisting of a 29.3 Mb terminal deletion of chromosome 18q21.2-qter and a 14.1 Mb terminal duplication of 20pter-p12.1. The pregnancy was terminated. Parental chromosome studies revealed a maternal 18;20 balanced translocation. Discussion: This case report demonstrates the potential for cfDNA screening to incidentally but accurately identify copy number variants when utilizing MPSS methodologies. These findings have significant clinical impact for patients and can provide important information regarding reproductive risks and options for the future. Incidental findings are not novel to cfDNA analysis; however cases like this reinforce the need for adequate pre- and post-test counseling and follow-up, as supported by the American College of Obstetricians and Gynecologists/Society for Maternal-Fetal Medicine joint committee opinion.

The Impact of Cystic Fibrosis on Women's Reproductive Decision-Making

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As women with cystic fibrosis (CF) live into their reproductive years with better health, the number of women considering pregnancy is also increasing. Research has shown that women with CF recognize that they lack adequate information about the effects of pregnancy on their health. Because pregnancy in any woman with a chronic illness can be complicated, having accessible information about how other women have made often conflicted decisions about pregnancy may benefit women with CF as well. The purpose of this study was to determine what factors impact the decision to try or not to try to become pregnant and how decisional conflict and cystic fibrosis-related quality of life relates to those factors. Women with CF over the age of 18 were recruited through various social media sites and completed an online survey that utilized two previously validated scales to assess decisional conflict and CF-related quality of life, as well as a scale that assessed the importance of various factors. Forty-three women between the ages of 20 and 59 completed the survey. Overall, major concerns included how pregnancy would impact their health and what impact their disease would have on their children. Several women (4/41) mentioned that having a negative carrier test for their partner reduced their anxiety about having an affected child and made them more likely to try to become pregnant. Analysis demonstrated no statistically significant differences of decisional conflict between women who decided to become pregnant, those who were undecided or decided not to get pregnant. Interestingly, two women who decided not to become pregnant had higher perceived quality of life and lower decisional conflict. By providing information about how others have made decisions, genetic counselors may promote informed decision-making to women with CF who are considering pregnancy and optimize both their health and quality of life.

How do Women Make Decisions About Preimplantation Genetic Screening? Sacrifices made and Factors Considered

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Pre-implantation genetic testing is a field in which research and techniques are advancing and uptake is increasing. Preimplantation genetic screening (PGS), in contrast to its counterpart, preimplantation genetic diagnosis (PGD), is a process by which embryos are screened for chromosomal aneuploidies prior to implantation into a woman's uterus for development. Implementation of ever-advancing technologies to screen embryos for chromosome aberrations through PGS has been shown to potentially increase pregnancy rates. Most research investigating decision-making related to preimplantation genetic testing has been focused on decisions regarding PGD (for families who are at risk for having a child with a specific genetic condition). Also, existing research focuses on couples who can easily access the technology (those of higher socioeconomic groups). The goal of this study was to assess women's opinions about PGS and the associated decisions made by women from a broader range of backgrounds, especially from varied socioeconomic (SES) groups. Fifty women, recruited through an infertility support group, completed surveys. Possibility of avoiding termination was rated as the strongest factor playing into decisions, but cost was consistently cited as a barrier to PGS. Thematic analysis was performed, which yielded 3 major themes: 1.) We'll try anything, 2.) Knowledge is power, and 3.) If we could afford it, we would do it. The majority of the women in this study indicated clearly that any technology that could increase the possibility of a euploid (and therefore, more likely healthy) pregnancy is worth pursuing, but that there are major barriers to the utilization of PGS technology. IVF/PGS was found to be financially inaccessible to women across a wide range of socioeconomic groups, including those of lower SES.

Efficacy of Genetic Testing in Cases of Ambiguous Genitalia Detected on Prenatal Ultrasound

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This study assessed the accuracy of genetic testing in identifying a prenatal diagnosis for ambiguous genitalia through a systematic review of published case studies and prenatal ambiguous genitalia identified cases from University Hospitals (UH) ultrasound database. Nine-thousand, three hundred and eighty-two articles were flagged for potential review. A total of 28 articles (2006–2014) met inclusion criteria. The 28 articles contained 89 case studies for review. The UH chart review yielded 39 cases from 2006 to 2014. Cases analyzed from the literature demonstrated that, regardless of which protocol was used, a prenatal diagnosis of ambiguous genitalia was correctly diagnosed in 60 % of cases. From these data, an algorithmic testing guideline was generated. Cases from the chart review that had prenatal and postnatal records were used to assess the efficiency of the proposed algorithm of identifying the correct diagnosis and was successful in 10 of 15 cases (66.6 %), with 5 cases being unclear as to whether a diagnosis could be reached using the proposed algorithm.

The Value and Impact of Genetic Counseling Risk Assessment

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Referrals for reproductive/preconception Genetic counseling (GC) to Integrated Genetics were analyzed for the time period March 1, 2013 thru March 1, 2015. During this time, 17,926 patients were referred by a physician for a family history of a genetic disease, birth defect or intellectual disability. Risk was assessed for all patients based on relevant family history information, medical records and review of genetic testing results. 4,632 patients were seen for a family history of a chromosome abnormality. 829 of these patients (17.9 %) were found to have no increased risk for a fetus with a chromosome abnormality based on the GC risk assessment. 8,994 patients were seen for a family history of a genetic disease. GC determined that 342 patients (3.8 %) did not have an increased risk for the genetic disease listed as the reason for referral. 3,433 patients were seen for a family history of physical birth defects. GC determined that 523 (15.2 %) of patients did not have an increased risk for the birth defect indicated in the genetic counseling referral. 867 patients were seen for a family history of intellectual disability. 407 patients (47.3 %) did not have an increased risk for intellectual disability based on the risk assessment. Genetic testing for the disorder identified as the referral indication was offered when an increased risk was identified. Genetic counseling risk assessment was more likely to identify an increased risk to patient's offspring when the referral was for a specific genetic disease, and was less likely to identify an increased risk when the referral indication was more general, such as intellectual disability. Genetic counseling improved accuracy of risk identification compared to physician referral indication ($r=-0.1519$). This study of data from a large genetic counseling program illuminates the value of genetic counseling in the provision of personalized genetic risk assessment and the identification of appropriate genetic testing.

Newborn Screening Education in the Prenatal Period: New Parent Experiences and Desires

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Newborn screening (NBS) has a history of occurring routinely without significant discussion or consent. The Minnesota NBS Program has recently begun to recognize the importance of early education to allow parents to absorb information before the hectic hours after delivery. These internal motivations to educate early were compounded by a state legislative mandate directing the NBS Program to provide prenatal providers NBS educational materials for use in the prenatal timeframe. We embarked on a new initiative to discover what expectant parents want to know and learn before screening occurs so we could tailor efforts. During the summer of 2014 we received 1,170 responses from new parents when asking about their recent experiences and desired experiences regarding newborn screening education in the prenatal period. Reported awareness of NBS prior to receiving the survey was high (89 %), but we found significant gaps between actual and desired educational experiences on the topic of screening. About half of expectant parents (51 %) reported learning about NBS from a nurse, although a majority of parents reported wanting to hear this from higher level practitioners, such as obstetricians/gynecologists and family physicians (68 % and 24 % respectively). Parents most frequently reported receiving information about NBS during labor and delivery (63 %), but nearly all reported wanting this information prenatally (93 %), especially during the 3rd trimester (64 %) of pregnancy. A majority (70 %) reported wanting to have a conversation about NBS with their provider, but only 61 % reported having that conversation with their provider. Lastly, we found that the content of current discussions about NBS lack key pieces of information that parents report are important to them. This includes how parents get results (76 % desired, 27 % received) and what happens when a result is abnormal (75 % desired, 26 % received). Overall, data suggests parents are not receiving the education they desire. These findings have implications for future medical practice regarding NBS education.

A False Positive Noninvasive Prenatal Screening Result Leads to an Incidental Finding of Translocated Yq Material in a Phenotypically Normal Female

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Noninvasive prenatal screening (NIPS) has become an increasingly popular tool for the screening of autosomal aneuploidy, sex chromosome aneuploidy, and recently, a limited number of microdeletion syndromes. These tests rely heavily on bioinformatics for interpretation and can provide seemingly inconsistent or equivocal results in comparison to diagnostic cytogenetic testing. In some cases, diagnostic cytogenetic testing may lead to the identification of a complex incidental finding.

Here, we report a case in which a pregnancy was screened via NIPS through two separate laboratories. Both NIPS reported findings suggestive of Klinefelter syndrome with greater than 99 % accuracy. However, ultrasound findings throughout the pregnancy were suggestive of a female fetus, and at birth, the newborn appeared to be a phenotypically normal female. Baby girl was reported to be healthy, non-dysmorphic, and was released from the hospital at the typical time. Chromosome studies were performed to confirm the sex chromosome content. Karyotype performed on peripheral blood revealed a derivative chromosome 22 with Yq material present on the short arm. Further discussions with the NIPS laboratories revealed that the amount of Y material detected was reportedly less than is seen in a true positive Klinefelter syndrome case. This case report emphasizes the importance of correlation of additional phenotypic findings and necessity of diagnostic chromosome studies to confirm NIPS results. Furthermore, while aneuploidies due to translocations are less common, provision of accurate data suggesting an unbalanced translocation will allow tailored counseling and discussion to occur upfront with the patient and their family. It also highlights the need for improvement of biostatistical analysis tools to discern partial aneuploidies from full aneuploidies.

A Crossroads: Noninvasive Prenatal Screening Microdeletion Syndromes Identified in Products of Conception Samples

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1. Natera

Objective: Report incidence of microdeletion syndromes screened for by noninvasive prenatal screening (NIPT) in a cohort of 17,424 products of conception (POC) samples. Purpose: No prior studies have examined the rate of syndromic microdeletions (1p36 del, Cri du Chat, Angelman, Prader Willi and 22q11.2 del) in miscarriage. In order, published live birth rates for these conditions are: 1/5000; 1/20,000; 1/12,000; 1/10,000; 1/2000. Methods: Retrospective review of 17,424 fresh POC samples shipped with maternal blood samples to a reference lab for analysis. Genotyping was performed using Illumina CytoSNP-12b microarrays with bioinformatics. Results: 14,824 cases (84 %) had fetal results, of these, 31 (0.2 %) had one of the above microdeletion syndromes; some had additional findings (AF) which may be related to the cause of the loss or incidental: 1p36 del (6 cases, 3 had AF, incidence 1/2470); Cri du Chat (12 cases, 6 had AF, incidence 1/1235), Angelman (2 cases, 2 had AF, incidence 1/7412), Prader Willi (3 cases, 2 had AF, incidence 1/4941); 22q11.2 del (8 cases, 2 had AF, incidence 1/1853). Median gestational age for these cases was 7 weeks. Conclusions: Higher incidences of syndromic microdeletions were found in this study of POC samples compared to reported live birth rates. Research into syndromic phenotypic variability by gestational age and relationship to causality of miscarriage is needed. This data may allow better recurrence risk counseling for families with a pregnancy affected with one of these syndromes, some of which carry significant recurrence risk based on potential parental chromosome anomalies or rearrangements. Future studies can compare these rates to other gestational age samples from NIPT, done as early as 9 weeks, and prenatal diagnosis offered later in gestation.

Obstetrician and Gynecologist Utilization of the Noninvasive Prenatal Testing Expanded Testing Option

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Noninvasive prenatal testing (NIPT) enables the detection of common fetal aneuploidies such as trisomy 21, trisomy 18, trisomy 13, and sex chromosome abnormalities via analysis of cell-free fetal DNA circulating in maternal serum. Although the accuracy of NIPT for fetal aneuploidy is expected to be higher than that of currently available alternative maternal serum screening options, the implications of results are not straight forward. In October 2013, the option to screen for additional trisomies and select microdeletion syndromes, such as 22q11.2 deletion syndrome and 5 p- syndrome, became clinically available. Due to this rapidly evolving prenatal screening technology, clinicians must make a conscious effort to keep abreast of the current options; however, the complexity of the testing methods, oftentimes unclear clinical utility of results, and current lack of professional guidelines for its use renders this task challenging. To assess physicians' awareness of, utilization of, and attitudes toward the expanded NIPT option, 85 Houston, Texas area Obstetrician/Gynecologists (Ob/Gyns) were surveyed. While all respondents indicated they were aware of NIPT in its traditional form, 75 % were aware of the expanded testing option. Of these respondents, 17 % report having elected the expanded testing option when ordering NIPT. Thirty-nine percent of those surveyed indicated they would feel at least somewhat uncomfortable explaining the expanded testing option to a patient and, accordingly, 91 % expressed that practitioners need more information regarding the screen. The responding Ob/Gyns indicated that this new screening option will be increasingly applicable to their future practice, with 28 % indicating that they plan to incorporate the NIPT expanded testing option into their practice in the future. Based on these findings and the quickly evolving landscape of prenatal screening, education and reeducation of healthcare professionals is imperative to ensure responsible patient counseling, informed consent, and appropriate management following test results.

Correlation of Occult Maternal Colon Cancer with Serial Noninvasive Prenatal Test Screening Evaluations

K. Murray[1]

1. Women's Care

Noninvasive prenatal testing (NIPT) is a revolutionary technique to screen pregnancies for common trisomies. The low false positive rate and very high detection rate has resulted in widespread use. This case illustrates the possibility that the unique nature of NIPT screening (genome wide copy number variants) may be associated with the genetic instability seen in cancer cells. Initially, the discordant NIPT and fetal karyotype results were likely to be explained by an expected mechanism such as confined placental mosaicism. However, this was ruled out. Approximately 10 months later, her colon cancer was diagnosed. Two more samples were obtained before and after her cancer treatment. Extensive bioinformatics analysis revealed more extensive copy number variation and the eventual return to normal after the treatment was completed. Occult maternal cancer may, 1 day, be found to be a possible explanation of discordant results.

Transitioning Cell Free DNA Testing for Aneuploidy to a General Pregnancy Population: Preliminary Results of the Rhode Island Experience

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Introduction: Cell free (cf) DNA testing for aneuploidy in high-risk settings has been validated by comparison with fetal karyotype. Professional societies now seek evidence of effectiveness in a general risk setting. Purpose: To introduce cfDNA testing through primary care obstetrical providers and document patient knowledge and decision-making in a subset of 3,000 women screened. We address provider and patient education and whether information was understood. We also developed a plan to manage DNA test failures. Methods: Targeted educational materials were created and validated. A protocol (DNAFirst) was implemented to offer cfDNA to all pregnant women, reflexing to serum screening and repeat cfDNA options for DNA test failures. Patients chose whether to include testing for sex chromosome aneuploidies. In September, 2014, following office education, DNAFirst was offered through providers at no charge to the patient or her insurance (via Natera, Inc., San Carlos, CA). Results: Through April 2015, 14 practices were approached, 12 were trained and 11 offered DNAFirst through 58 providers without additional office resources. Of the 1,904 women tested, 62 % were drawn at 11–12 weeks and 78 % were <35 years of age. Most women (91 %) opted to include sex chromosome aneuploidy testing. The cfDNA positive rate was 1 %(19/1914): six T21 (4 true positive (TP), 1 false positive (FP), 1 pending), two T18 (1 TP, 1 pending), three T13 (1 TP, 1 FP, one probable), five sex chromosome aneuploidy (2 confirmed, 3 pending),

and three triploidy/twin (3 twins [2 vanished, 1 not previously known]). There were 1,779 negative results and 106 DNA failures (5.5 %). Among failures, 68 had a normal repeat DNA or serum result, yielding a revised rate of 1.8 % (some results pending). Conclusions: General primary care obstetrical providers are capable of offering cfDNA testing given proper education. Sample drawing and handling do not pose significant logistic issues. False positive rates are low, with very few women recommended for diagnostic testing, and positive predictive value high (82 %, excluding twins and pending cases).

Genetic Conditions in Congenital Diaphragmatic Hernia and Recommendations for Prenatal Testing

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Introduction: Congenital diaphragmatic hernia (CDH) occurs in 1 in 3,000 pregnancies and causes significant neonatal morbidity and mortality. In approximately 40 % of cases there is an additional malformation, and in 10-15 % of cases there is an associated genetic syndrome. Identification of a genetic syndrome is important in counseling about expected prognosis. Methods: We retrospectively reviewed 97 cases of prenatally diagnosed CDH. All had an additional malformation and/or genetic condition. We assessed the types of syndromes, method of diagnosis, and outcome. Results: Chromosome abnormalities were present in 14/97 (14 %), which were very variable. Two were 15q26 deletions, and one was ring chromosome 15. A single-gene condition was identified in 9/97 (9 %) cases, either through molecular confirmation or clinical suspicion. Cornelia de Lange was identified in three cases. Other syndromes included Goltz, Fryns, Beckwith-Wiedemann, and Donnai-Barrow. Heart defects were present in 50 cases, and complex heart disease was a poor prognostic indicator. Other malformations included omphalocele (8), limb defects (6), renal abnormalities (6), and urogenital abnormalities (4). Discussion: There are a variety of genetic conditions to consider when providing prenatal genetic counseling for CDH. In our series, only 3 of the 14 chromosomal abnormalities would be detected using cell free fetal DNA testing. Additionally, some of the chromosomal abnormalities that were identified can be missed on routine chromosomal analysis. Amniocentesis with high resolution chromosomal microarray (CMA) is recommended. Many single-gene genetic conditions were seen with Cornelia de Lange as the most frequent. This condition should be considered if chromosomes and CMA are normal, especially if there is IUGR. Although Fryns syndrome and Donnai-Barrow syndrome have strong associations with CDH, these two conditions are very rare and they were not the most frequent syndrome reported in our series.

Amniocentesis does not Increase the Risk of Miscarriage in a Screen Positive Population when Performed by an Experienced Practitioner

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Objective: In order to provide more appropriate counseling to women with a prenatal screen positive result regarding the risk of miscarriage after amniocentesis, we compared the rate of pregnancy loss in women that elected amniocentesis (14–24 weeks GA) to women who declined diagnostic testing. Study Design: Patients with a screen positive result from the California Prenatal Screening Program are offered referral to a Prenatal Diagnosis Center, where follow-up services include genetic counseling with a detailed ultrasound and amniocentesis by an experienced practitioner, if indicated. Pregnancy outcomes/losses were ascertained by postpartum surveys sent to providers of screen positive patients. Cases with confirmed chromosome abnormalities or birth defects were excluded, as were cases that were screen positive for neural tube defects based on the difference in amniocentesis acceptance rates in this group. The outcomes of women with singleton pregnancies electing amniocentesis were compared with those that declined. Two-sided confidence intervals for the loss rates in the two groups were calculated. Results: After exclusions, there were 11,478 amniocenteses and 14,475 declines that were screened between April 2009 and December 2012. In the amniocentesis group, there were 80 fetal losses (0.70 %, 95 % CI 0.54–0.85 %). In the decline group, there were 117 fetal losses (0.81 %, 95 % CI 0.66–0.95 %). These rates were not significantly different (p=0.84). Conclusion: Screen positive women who had amniocentesis with an experienced practitioner were not at increased risk for miscarriage/fetal loss compared to women who declined the procedure. The risk after amniocentesis is also lower than what most counselors describe to patients. This population is at increased risk for adverse outcome related to abnormal maternal serum analyte levels and counseling should address this risk more so than the risk of miscarriage from amniocentesis. In our study, there is no evidence that amniocentesis by an experienced practitioner increases the risk of fetal loss.

Women's Assessment of Benefit in Pre-Test Genetic Counseling for Noninvasive Prenatal Testing

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Objectives: Kaiser Permanente Southern California currently offers noninvasive prenatal testing (NIPT) as a screen in all high-risk pregnancies. Prior to screening, patients receive a one-hour, individual consult on screening and diagnostic options. To assess the value of this resource-intense model, this study tests women's evaluation of benefit in extended, pre-test genetic counseling. Method: Self-administered survey methods were used for data collection with pregnant women eligible for NIPT referred to one of two genetic counseling practices in Southern California. Women were asked to complete surveys after their genetic counseling session. Results: The average age of 336 respondents was 37 years and 11.5 weeks gestation; response rate was 76.4 %. Almost all women reported that pre-test genetic counseling was 'extremely' or 'very' helpful (93 %) in deciding whether or not to have NIPT. Semantic differential formatting of 1 (very clear) to 7 (very confusing) found that over 73 % of women reported pre-test counseling made their options 'very clear'. On a similar rating, 76.5 % of women reported counseling made them feel more calm than anxious. Of the 64 % of women who reported only a little or no understanding of NIPT prior to counseling, almost 86 % reported that the consult helped their understanding of NIPT 'a lot'. 80 % of women reported little or no understanding of conditions tested for by NIPT prior to counseling and said that the consult helped their understanding 'a lot'. Post counseling, women overwhelmingly reported feeling more certain about what they would do next if their NIPT results were returned as normal (96 %) or abnormal (93 %) respectively. Conclusion: Women found extensive, pre-test genetic counseling useful in their decision-making around NIPT, suggesting that that this model should remain the gold standard in counseling for NIPT.

Newborn Screening Education in the Prenatal Period: Provider Practices and Desired Assistance

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Since its inception more than 50 years ago, newborn screening (NBS) has been a routine standard of care. Yet while screening happens routinely, it is imperative that parents are informed about this life-saving process. In 2014, the Minnesota Legislature passed a law mandating the Newborn Screening Program to provide education materials to prenatal providers for use in educating about NBS. In order to assess what providers truly want and need from the Program, we surveyed prenatal care providers and received responses from 396 providers about their current educational practices and any additional needs for outreach and/or materials they may have. Our results showed that labor/delivery and postpartum are the most frequently reported timeframes for educating patients about NBS (85 %), and that a small minority of providers report never discussing NBS with their patients (6 %). A significant number of respondents (35 %) report that they do not feel sufficiently informed about NBS and that this poses a barrier to educating their patients about the topic. When asked what additional provider-specific resources would aid in patient education, providers indicated that they desired: written materials (54.8 %), website links (43.9 %), pocket cards (39.9 %), and phone applications (33.8 %). When asked what patient-specific resources would aid education efforts, providers indicated that they desired: written materials (78.3 %), tear-off fact sheets (53.0 %), a short video (46.0 %), and website links (45.2 %). These findings suggest that while prenatal providers report education is occurring for most patients, a significant number of providers do not feel sufficiently informed about NBS, and there are a number of resources health departments can develop to better assist their medical partners in educating expectant parents about NBS. These findings have important implications for future health department practices regarding intentional development of materials for prenatal provider audiences.

Cerebellar Hypoplasia Associated with Mutations in the EIF2B2 Gene

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Prenatal diagnosis of cerebellar hypoplasia (CH) is a relatively common, but non-specific neuroimaging finding. The etiological spectrum of CH is wide and includes both primary (malformative) and secondary (disruptive) conditions. Primary conditions include chromosomal (e.g., trisomy 13, 18), metabolic disorders (e.g., molybdenum cofactor deficiency, Smith-Lemli-Opitz), genetic syndromes (e.g., Joubert, CHARGE), and brain malformations (primary posterior fossa malformations or global brain malformations). Secondary conditions include prenatal infections, teratogens, and prematurity. We report on a couple with two pregnancies with CH presenting in the second trimester. Their first pregnancy was complicated by oligohydramnios, microcephaly, CH, mega cisterna magna, single umbilical artery, and intrauterine growth restriction (IUGR). The couple terminated the pregnancy. Amnio showed a normal karyotype (46,XY); autopsy was declined. In a second affected pregnancy, Integrated Prenatal Screening was positive for trisomy 18. Detailed fetal ultrasound at 18.5 weeks showed oligohydramnios, IUGR, CH and prominent cisterna magna. MRI at 21 weeks showed a small cerebellum and disproportionately large cisterna magna. The couple terminated the pregnancy. Whole exome sequencing on DNA from the second affected fetus identified compound heterozygote mutations in the EIF2B2 gene; each parent was heterozygote for a mutation. A healthy sib was heterozygous for the paternal mutation. Mutations in the five EIF2B subunits (including *EIF2B2*) have been described in association with a group of leukoencephalopathies that includes the CACH syndrome (Childhood Ataxia with Central nervous system Hypomyelination) or Vanishing White Matter, with mutations in the EIF2B5 gene being the most common. A wide clinical spectrum exists within this group, from severe, lethal infantile forms to adult-onset forms with slow progression. To the best of our knowledge, this is the first reported case of prenatal presentation within the EIF2B leukoencephalopathies, and provides insight into the prenatal phenotype associated with mutations in *EIF2B2*.

Clinical Experience with a Single Nucleotide Polymorphism (SNP) -Based Noninvasive Prenatal Test for 22q11.2 Deletion Syndrome

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Introduction: The occurrence of 22q11.2 microdeletions (associated with DiGeorge syndrome) is independent of maternal age. Because of their small size, these deletions are more difficult to detect by noninvasive prenatal testing (NIPT). Purpose: To report on the clinical experience with our single nucleotide polymorphism (SNP)-based NIPT for this microdeletion. Methods: 20,776 consecutive, eligible, maternal blood samples were received between February and August 2014. A unique set of PCR primers amplified 672 SNPs in the 2.91 Mb DNA segment commonly deleted in this syndrome. Sequencing and analysis of the SNPs allowed determination of fetal and maternal copy number at the interrogated region. 19,237 cases received a high-risk or low-risk call for the presence of this deletion. Follow-up information was sought for all high-risk cases. Results: 95 (0.5 %) pregnancies were found to be high risk for a 22q11.2 deletion. In two additional cases, the mother was suspected to have the deletion; one of these was confirmed and one likely based on family history. Diagnostic testing was obtained for the fetus in 61 high-risk cases: 11 were true positives and 50 were false positives, resulting in a positive predictive value (PPV) of 18.0 %. Re-sequencing 89 high-risk samples at a higher depth of read (i.e., reflex testing) improved the PPV to 42.3 % (11/26). Invasive testing decisions were known for 84 cases: 57.1 % (48/84) had invasive testing and 42.9 % (36/84) declined. Ultrasound anomalies were present for 81.8 % of true positives and 18.0 % of false positives. The PPV for cases without known ultrasound findings prior to NIPT was 5.1 %; this increased to 16.7 % following reflex testing. Conclusions: Screening for 22q11.2 deletion syndrome with this SNP-based NIPT resulted in a 0.5 % rate for high-risk calls with a PPV of 18.0 %. Early therapeutic interventions exist and can substantially improve the quality of life for the affected child. The routine provision of prenatal screening for 22q11.2 microdeletions should be considered for women already undergoing NIPT for fetal aneuploidy.

Exploring Birthparent's Experiences of Creating an Adoption Plan for Their Children with Down Syndrome

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Introduction: Very little peer-reviewed information is available regarding the experience and needs of families who create an adoption plan for children with disabilities. The purpose of this study was to learn more about the experiences of birthparents who created an adoption plan for their child with Down syndrome (DS) in order to understand their informational and emotional needs for decision-making and throughout the adoption process. Methods: Birthparents were invited to participate in the study by membership emails from the National Down Syndrome Adoption Network (NDSAN). Information about the study was also made available on the organization's website. Semi-structured telephone interviews were conducted with five birthmothers who had created adoption plans for their children with DS. Conventional content analysis methods were used for systematic coding and identification of emergent themes. The interviews focused on three major areas: (1) families' reasons for creating an adoption plan, (2) informational and emotional needs of these families, and (3) messages to other birthparents and medical health professionals about special needs adoption. Results: All five birthmothers were Caucasian, over 35 years of age, and all but one were married with previous children. Various reasons for creating an adoption plan included unplanned pregnancy, feeling unprepared to raise a child with DS, and religious or personal beliefs regarding pregnancy termination. Finding the "right" adoptive family was identified as an instrumental factor for finalizing the adoption plan. Emotional and informational needs included support from their partners, acceptance from others, informational resources about the process and the opportunity to connect with other birthparents who had been through the same situation. Conclusion: Consideration of these results may help genetic counselors and healthcare providers to facilitate informed decision-making and may also bring greater ease during the discussion about adoption with families who may have not otherwise considered adoption.

Whose Y is it Anyway? Transplantation as a Biological Cause of Noninvasive Prenatal Testing Gender Discrepancies

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Introduction: Since the introduction of noninvasive prenatal testing (NIPT) in 2011, more than 400,000 clinical samples have been run in Sequenom Laboratories. Discrepant results often have biological explanations, including confined placental mosaicism, maternal mosaicism, co-twin demise, and maternal neoplasm. As cell-free DNA is comprised of maternal and trophoblastic placental DNA, tissue from foreign organs can contribute its DNA to the pool. Here we describe three cases of NIPT fetal sex discrepancies in patients who had undergone bone marrow and liver transplants. Methods: Maternal blood samples submitted to Sequenom Laboratories for ccfDNA testing were subjected to DNA extraction, library preparation, and whole genome massively parallel sequencing as described by Jensen et al. Sequencing data were analyzed using a novel algorithm to detect certain aneuploidies and microdeletions as described by Chen et al. Case#1: NIPT result: Male, negative for aneuploidies. Provider informed us that ultrasound was consistent with a female fetus. Second aliquot of sample was run. Both samples showed a strong Y signal. Provider later informed the lab that the patient had a liver transplant due to Wilson's disease 16 years prior, from a male donor. Case#2: NIPT result: Male, negative for aneuploidies. Provider informed us that ultrasound was consistent with a female fetus. Provider later informed the lab that the patient had a bone marrow transplant from her brother in 1985. Normal female anatomy at birth. Case #3: NIPT result: Male, negative for aneuploidies. Provider informed us that ultrasound was consistent with a female fetus and that the patient had a bone marrow transplant from her brother in 2002 due to aplastic anemia. In reviewing the data, the sample showed a strong Y signal. Conclusion: Obtaining a detailed clinical history in cases of NIPT discrepancy can provide unexpected and valuable clues toward resolution and understanding. As NIPT becomes increasingly available to all populations, pre-test counseling about maternal conditions is essential.

Professional Issues

An Exploration of the Roles and Satisfaction Level of Genetic Counselors Working with Newborn Screening

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Introduction: Newborn screening (NBS) is a public health service administered by Newborn Screening Programs in all 50 states, as well as many international locations. Through this screening, newborns at risk for serious conditions are identified, evaluated, and those with confirmed disease receive timely treatment. Genetic counselors (GCs) may be involved with NBS through direct work with a Program, designated evaluation and treatment centers, or via other means. The purpose of this study was to elucidate the roles of these counselors, and their satisfaction with this work. Results: A 29-question survey was distributed via email to the Association of Public Health Laboratories (APHL) Newborn Screening Technical Assistance and Evaluation Program (NewSTEPS) listserv as well as an international listserv administered by the National Newborn Screening and Global Resource Center. In total, 69 GCs responded, of which 97 % were female, 71 % were ages 25–44, and 49 % had graduated from their training program within the last 10 years. In their NBS roles, 25 % were the first GC in that position, 39 % worked in role for 1–5 years, and 78 % had a clinical role prior to NBS work. In their NBS role, 77 % of respondents had face-to-face patient contact, 97 % had telephone contact with patients, and 69 % have been involved in education via presentations and/or material production. The majority of respondents worked with the Inherited Metabolic Disorders (79 %) and/or Cystic Fibrosis (71 %), and 28 % have supervision responsibilities in their NBS role. 84 % of respondents said they were moderately or completely satisfied with their NBS role, and 95 % said they would recommend this work to other GCs. Individual factors such as work schedule, respect from co-workers, utilization of GC skills, and intellectual stimulation rated highest satisfaction levels; opportunities for advancement had the lowest rate. Conclusions: Genetic counselors working with newborn screening have high rates of satisfaction with this work.

Misconceptions and Psychosocial Issues Raised by Linkage Analysis Completed in 1987: A Case Report

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We report the case of a patient who presented with a striking family history of breast cancer. The family history was notable for four out of her five brothers having died from an unknown muscular dystrophy (ages of death ranged from 19 to 43). All were confined to wheelchairs, did not have use of their legs, and were never given a diagnosis. The family had linkage testing performed in 1987 that was inconclusive suggesting linkage to the DMD locus. However, the family had an incorrect impression that the test was conclusive and identified the carriers and non-carriers in the family. The proband was diagnosed with cardiomyopathy. The family's pedigree suggests an x-linked muscular dystrophy with symptomatic carriers. Due to the concern about the possibility that the proband could be a symptomatic carrier, genetic testing was ordered for the proband. Intricate psychosocial issues were raised by the family's impression

of a 'conclusive' test. We educated the family about the limitations of the previous testing done and explained the implications an X-linked muscular dystrophy could have for carriers. This case exemplifies the importance of pre- and post-test counseling and demonstrates the massive strides genetic counseling has made since 1987. Genetic counseling helped clarify this family's medical history, genetic testing misconceptions, and integrated this family into their own medical care.

Seekers, Finders, Settlers, and Stumblers: Identifying the Career Path for Males in the Genetic Counseling Profession

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Introduction: Genetic counseling is a female-dominated profession, as 96 % of counselors self-identify as female. Prior studies suggest gender diversification benefits both members of a profession and populations they serve. The aims of this study were to explore men's reasons for choosing a genetic counseling career, and associations between career entry dynamics and career satisfaction. Methods: Twenty-five male counselors (with 0–5, 6–14, or >15 years experience) and 8 male genetic counseling students, recruited through NSGC and program directors, participated in semi-structured phone interviews. Inductive and cross-case analysis of interview data was informed by Simpson's "Seekers, Finders, and Settlers" theory about men in non-traditional careers. Results: Fourteen interviewees (42 %) were seekers, who actively chose a non-traditional career; 10 (30 %) were settlers, who tried various traditional jobs with limited satisfaction before settling into genetic counseling; and two (6 %) were finders, who discovered genetic counseling while making career decisions and had no desirable alternative. Seven men (21 %) fit a new category, we termed stumblers, who were already pursuing another career path before hearing of genetic counseling, at which point they actively pursued it. Prevalent career entry dynamics included: desire for a multidisciplinary career; lack of knowledge of different genetic counselor roles; and initial exposure to the profession following graduation from college. Many individuals chose genetic counseling as they did not find "the right fit" in medical school or laboratory research. Career satisfaction was high across cohorts and regardless of how one entered the field. Discussion: Few males actively sought a genetic counseling career, suggesting a need for exposure to the profession earlier in one's education, and more detailed descriptions of multidisciplinary aspects of the career.

The Evaluation of the Molecular Basis of Disease (EMBoDy) in Clinical Reporting: What Genetic Counselors Need to Know for Counseling and Return of Novel Genetic Etiology Results Identified via Diagnostic Exome Sequencing

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Exome sequencing serves a dual role as a diagnostic and a discovery tool, and case reports of patients in whom a novel genetic etiology is identified on a clinical basis are becoming abundant. A novel genetic etiology is a newly described gene-disease relationship. In our laboratory, a novel genetic etiology is reported in ~10 % of patients. The analysis and assessment criteria used to evaluate novel genetic etiologies for clinical reporting are markedly different than those used for a clinically characterized gene. Given the implications for genetic counseling, it is important for genetic counselors to be aware of these differences. Overall, the evidence criteria used to report a novel genetic etiology is much more stringent than a characterized gene finding. For alterations in characterized genes in which the patient's phenotype is consistent with the known clinical and molecular spectrum, the reportable findings are categorized as positive, likely positive, or uncertain. Because no previous patients have been reported for novel genetic etiologies, a unique set of scientific criteria are used to make the case for the gene's potential implication in the patient's phenotype. Evaluated evidence includes relevant human microdeletion syndromes, gene function and expression profiles, co-localization/interaction with gene products known to cause similar presentations, animal models, gene family/pathway information, and possible mutational mechanism inferred from distribution of variants in control populations. If there is sufficient, high quality evidence, findings are reported out as either likely or possibly positive. The remaining novel gene findings with insufficient available evidence are provided in a supplemental list in the patient's report. These are not negative findings, and the possibility exists for sufficient scientific evidence to emerge in the future. Therefore, it is important for the genetic counselor to remain in contact with the laboratory to gain new information, to perhaps find additional patients with alterations in the same gene.

An Exploration of the Nuances of Common Legal Documents Commonly Encountered in Industry-Based Employment Settings

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1. Invitae

The Supreme Court's decision that naturally occurring genetic material cannot be patented removed a longstanding hurdle to innovation in and expansion of clinical genetics. This, in turn, is fueling the growth of the genetic counseling profession, which is rapidly forging paths beyond the clinic, opening exciting opportunities as well as unique challenges for the profession. In particular, an increasing number of genetic counselors are accepting positions in private industry. Here we present an overview of issues that are not often taught in genetic counseling training programs and often not appreciated by professionals before accepting positions in industry. While there are clearly exciting opportunities in industry, there are important issues that run the gamut from restrictive clauses in employment contracts, such as non-competes and confidentiality, to at-will employment, conflicts of interest, and up front promises to transfer ownership of intellectual property. Education on these topics is essential for genetic counselors to better appreciate how best to uphold a high standard of practice while adhering to industry norms, and exploring new disciplines. Understanding the nuances of the legal documents is an important step for genetic counselors as more companies in industry are relying on their expertise as a key strategic element to commercial success. It is mutually beneficial if the profession is as savvy about best practices and obligations to the workplace as they are prepared to uphold their high standards of practice. Genetic counselors should increase awareness of their obligations to both their profession as well as their employer in terms of details outlined in employment documents. By providing genetic counselors with a neutral, fact-focused overview of the legal requirements upon hire, it is our goal to provide them with educational resources and tools for which they can approach these commitments with a better overall understanding, in turn leading to an informed career path.

Measuring Awareness and Perceptions of Genetic Counseling in Three Groups: General Population, a Disability Community, and a New Parent Community

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Background: Understanding awareness and perceptions of genetic counseling (GC) among different groups is important in order to identify and overcome potential barriers to GC services. However, there are relatively little empirical data regarding awareness and perceptions of GC among US-based populations. Methods: To address this gap within the state of California, we attended community events for the general public, disability community, and new parents, and recruited people to participate in a survey-based study comprising demographic questions, closed-ended knowledge-based and awareness questions, and open text sections. We applied descriptive statistics to responses about: demographics, whether the individual had heard of GC, and perceptions of what a genetic counselor does. Open text responses to a question about participants' first associations with the phrase "genetic counseling" were analyzed for themes. Responses to 18 items about the possible purposes of GC were used to generate a total "knowledge score". Results: In total, 320 people participated, including 69 from the general public, 209 from the disability community, and 42 from a new parent community. Slightly more than half of all respondents (n=173, 54 %) had heard of GC. Risk assessment and counseling were amongst the most frequently cited activities attributed to genetic counselors, but a small number felt that GC was related to eugenics. Many respondents thought that GC aims to prevent genetic diseases and abnormalities (n=82, 74 %), help people find their ethnic origins and understand their ancestry (n=176, 55 %), advise people about whether to have children (n=140, 44 %), and help couples have children with desirable characteristics (n=126, 39 %). The mean knowledge score was 12/18 for all groups combined, and scores were not significantly different between communities or any demographic groups. Conclusions: These data reveal gaps in awareness of GC and misperceptions about its purpose. These data could be used to develop targeted interventions to improve awareness and dispel misconceptions.

Spanish-Speaking Medical Interpreters' Understanding of and Attitudes Towards Genetics and Genetic Counseling

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Background: The need for spanish-speaking medical interpreters can be demonstrated ethically, statistically, and legally. While many studies have researched interpreters in other medical specialties, there is a lack of literature regarding interpreters in genetics and genetic counseling sessions. Purpose: This exploratory project aimed to address the following research questions: What do interpreters know about genetics and genetic counseling, and where do they obtain this education? What do interpreters understand about the importance of genetics and genetic counseling? What attitudes do interpreters have about genetics and genetic counseling? Methods: This study was conducted through telephone interviews with spanish-speaking medical interpreters recruited through three interpreter organizations in the Triad region of North Carolina. Nine participants completed telephone interviews. Interview responses were analyzed qualitatively by thematic analysis. Results: Participants reported that genetic counseling is important because of patient education, psychological counseling, follow-up care, and patient decision-making. The most common perceived barriers to nondirectiveness included patient education level and health care provider characteristics. Terminology was the most frequently reported challenge for interpreting in genetic counseling sessions. Sources of genetic counseling knowledge included previous science classes, previous interpreting experiences in genetic counseling, the Internet, and interpreter training. Discussion: Interpreters demonstrated a general knowledge and understanding of genetic counseling and its importance, but most lacked knowledge of the intricacies of the profession. The majority of participants discussed the importance of interpreter education in genetics and genetic counseling, and many expressed interest in training courses. All participants reported that genetic counseling was enjoyable and/or an important service. This information can be used to promote educational efforts for interpreters working with genetic counselors.

The GC on TV: The Absence of a Genetic Counseling Professional in Popular Medical Television Storylines and What we can do About it

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Background: Entertainment education is a means of informing the public about a social issue or concern that involves incorporating an educational message into popular entertainment content. TV is one vehicle for entertainment education that has the potential to reach millions of viewers at a time. Studies have shown that TV education entertainment can be used to raise awareness, increase knowledge, create favorable attitudes, and even motivate people to take health related actions. But there are no published data regarding representation of genetic counselors (GCs) in TV shows. Methods: First, we explored representation of GCs in mainstream TV shows that incorporate clinical genetics scenarios. Second, to establish interest in and preferences regarding a hypothetical genetic counseling themed TV show amongst potential audiences, we surveyed 320 individuals from three different groups: a disability community, a new parent community, and the general public. We asked respondents about how they consume their media, and what type(s) of programming they would prefer for a hypothetical genetic counseling themed TV show. Specifically, participants used a 5 point likert scale to rate their interest in watching (would definitely watch to would definitely not watch) hypothetical genetic counseling TV shows of the following types: talk show, reality, comedy, documentary, or medical drama/thriller. Results: We reviewed various clips from popular TV shows that incorporate clinical genetics and identified 6 specific instances in which a GC character could have been involved or written into a scene. However, to date, to our knowledge, no GCs have ever been portrayed or written into a TV show. Our survey data showed that the majority of participants in all groups preferred to watch a medical thriller followed by documentary series, and all groups rated the comedy the lowest. Conclusion: These data could be used to illustrate a niche content need to TV producers, and to inform the development of a show to teach the public about genetic health and the roles of GCs.

Exploring the Impact of Multiplex Cancer Gene Panels on Genetic Counselors: "I really didn't See this One Coming"

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Since 2012, advances in technology and research have led to the introduction of multiplex gene testing for cancer susceptibility in clinical settings. While this introduction has been viewed as a cost effective and efficient approach to testing, it has also yielded an increased number of unexpected results with unknown consequences for patients and providers. The goal of this study is to describe counselors' early experiences with multiplex cancer panels and to identify the needs of the counselors based on these experience. Semi-structured telephone interviews were conducted with members of the National Society of Genetic Counselors (NSGC) who specialize in cancer genetics about their most memorable

experience involving multiplex cancer gene panels; counselors were also asked about their experience receiving and interpreting multiplex gene panel results. Fourteen genetic counselors were interviewed. All of the counselor's memorable cases involving multiplex cancer gene panels were memorable due to an unexpected result. We categorized the counselors' reactions into three main types: frustration (expressed by 87.5 % of counselors), anxiety (71.4 %) and excitement (35.7 %). In this small study, it was found that the majority of counselors are ordering cancer gene panels regardless of their overall experience. Despite numerous challenges, when asked to sum up their experience with multiplex cancer gene panels, the majority of cancer genetic counselors view multiplex gene panels as a positive advancement to the field.

Responsibilities, Competencies, and Resources of Genetic Counselors in Management Positions

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Background: According to the Professional Status Survey produced by the National Society of Genetic Counselors (NSGC), the number of genetic counselors that hold managerial positions has increased over the past 4 years. While genetic counselors continue to expand into managerial positions, little is known about the responsibilities, competencies, or resources of these genetic counselors. Goals: The goals of this exploratory study were to 1) describe the responsibilities of genetic counselors in management positions; 2) evaluate the importance and frequency of use of Accreditation Council for Genetic Counseling (ACGC) Practice-Based Competencies (PBC) and select managerial competencies by genetic counselors in management positions; and 3) identify additional resources genetic counselors use to build their management skills. We hypothesized that genetic counselors use the core competencies they already possess when they transition to management roles. Methods: Online anonymous survey methods and semi-structured telephone interview methods were used to survey genetic counselors self-identified as holding management positions. Results: The 113 genetic counselors in managerial positions who completed the survey rated all ACGC PBC and all given managerial competencies above a rating of 2 (with 3 being the highest), indicating they are important and frequently used in their current positions. Mentorship and personal communication with other managers was rated as being the most valuable resource to participants in gaining managerial skills. Although the majority (64 %) of participants received on-the-job training in management skills, 83 % would have liked additional resources and/or opportunities for management training prior to beginning their current position. Conclusions: Genetic counselors report using their genetic counseling skills in their current managerial position, although they desire more resources and training in the area of management. A special interest group (SIG) through the NSGC may be one way managers can connect with mentors, gather resources, and identify additional training opportunities.

Provision of Genetic Services: Is it Time to Embrace Social Media?

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Social media is changing the way people interact with each other, including the manner in which healthcare providers interact with their patients. Technological advances are being made exponentially in all areas of healthcare and, to date, there have not been any published studies investigating patient-provider interactions between genetic counselors and their patients. The purpose of this descriptive study was to define current social media usage and interest in social media in the provision of genetic counseling services. The study aimed to 1) assess genetic counselors' use of, interest in, and challenges regarding using social media to interact with patients and other professionals; 2) assess patients' use of, interest in, and challenges regarding using social media to interact with clinical genetics professionals; and 3) compare use of social media, interest in using social media for clinical genetics services, and challenges associated with using social media for patient-provider interactions between the two groups. Genetic counselors who are members of NSGC (n=223) and genetics patients at University Hospitals (n=106) were surveyed on their current use of social media, interest in using social media for patient-provider interactions, and concerns and challenges for using social media in this way. This study found that 54 % of the patient population, compared to only 33 % of the genetic counselor population, reported interest in patient-provider on social media. The ability to maintain patients' privacy and confidentiality was ranked as a high level of concern by both groups. In addition, 55 % of genetic counselors thought it was somewhat or very important for NSGC to develop a policy statement addressing social media interactions with colleagues, and 89 % thought it was somewhat important for NSGC to develop a policy statement regarding social media interactions with patients. As both personal and professional interactions on social media continue to increase, genetic counselors will need guidance on how to respond to social media interactions from patients.

Incidental Misidentification of Constitutional Mismatch Repair Deficiency via Whole Exome Sequencing and its Impact on Management

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Introduction: The following case report illustrates whole exome sequencing's potential to identify incidental findings with substantial unforeseen clinical impact. It also describes the technical limitations of whole exome sequencing (WES), and how correct result interpretation greatly impacts appropriate patient care. Case report: JS was a 2 year old male whose family pursued WES at our clinic due to his history of seizures, GI dysmotility, laryngomalacia, and hypotonia. WES did not identify a diagnosis for the above symptoms, but reported a homozygous mutation in *PMS2*. This established the diagnosis of Constitutional Mismatch Repair Deficiency (CMMRD), which is associated with brain tumors, leukemia, lymphoma, small bowel and colorectal cancers. Prior to WES the personal or family history was not suspicious for CMMRD, but its identification indicated the need for an intensive screening protocol for JS. The testing facility did not disclose the mechanism of inheritance, but did not identify UPD or a *PMS2* deletion. Parental testing identified a mutation in JS's mother, which established the diagnosis of Lynch syndrome for her. However, JS's father did not have a *PMS2* mutation. JS was retested by a local genetics department using a separate facility, which identified the presence of a heterozygous *PMS2* mutation. This changed JS's diagnosis from CMMRD to Lynch syndrome, which is allows his cancer screening to be delayed until age 20. Discussion: This case illustrates WES's ability to identify incidental findings, and demonstrates the need for informed consent prior to testing regarding this potential. Through the reporting of these incidental findings JS and his family have the ability to receive tailored screening not evident by the personal and family history. Additionally, this case illustrates the need to counsel families of the limitations to the technology utilized by WES.

The Role of a Genetic Counselor as Coordinator and Clinical Recruiter in a Study of Hereditary Susceptibility to Lung Cancer

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A Genetic Counselor's (GC) experience and training provide the unique skills needed for coordination and recruitment of medical oncology patients into genetic research studies. For successful recruitment, the coordinator must possess: knowledge of cancer genetics, the ability to collect family health histories, and from those histories, determine on which family members to collect medical records and biospecimens for genetic analysis. Incorporating a GC for recruitment of patients into the Genetic Epidemiology of Lung Cancer Consortium (GELCC) study from the Lung Cancer Multidisciplinary Clinic at the Karmanos Cancer Institute/ Wayne State University School of Medicine during a visit with their oncologist proved to be highly beneficial. Lung cancer patients reporting a family history of lung cancer were asked for permission to meet with a GC Study Coordinator at the conclusion of their visit with an Oncologist. Approximately 90 % of patients approached in this way by the GC were receptive to discussing the study during their visit. The GC conducted the consenting process and coordinated biospecimen collection from the patient (probands) and their family members. During the recruitment period (1998–2012), about 80 families of the 600 total families collected at our site originated from clinical recruitment. The biospecimens collected have been a tremendous resource for linkage analysis, genome-wide association studies, and whole exome sequencing analysis, in addition, data have been provided to the National Institutes of Health bio-repository. As the recruitment phase ends, there continues to be a need for the skills of a GC to maintain data, manage medical histories, and facilitate the inclusion of this unique study population into behavioral and other relevant studies. In conclusion, the recruitment of participants by a trained GC in the setting of a Multidisciplinary Lung Cancer clinic proved to be highly effective.

Addressing Employer Needs by Meeting Employee Needs: Successful Integration of Teleworkers

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1. Mayo Clinic

Historically, the Biochemical Genetics Lab (BGL) at Mayo Clinic was supported by a team of onsite genetic counselors (GCs). In response to continued institutional growth and typical turnover, compounded by growing demands for GCs nationally, teleworker use was evaluated. To assess feasibility, the responsibilities of the BGL GCs were categorized into three primary groups of tasks that: 1) could be accomplished offsite, 2) could not or would pose difficulty, or 3) would require additional discussion. In addition, potential barriers and onsite:teleworker ratios were considered. After evaluating the daily team responsibilities, initial concerns were raised regarding the number of items which could not be performed by a teleworker. However, after extensive review of how duties were performed it was found that the majority could be done with minor modifications. Those remaining were primarily team building or professional enhancement activities. The times and reasons a teleworker would need to physically be at the laboratory were anticipated. The largest onsite time commitment was for training. The structure of these visits varied depending upon previous laboratory experience. Multiple trips were required which allowed new GCs to gain specific skills and put them into practice at their offsite work locations. The hiring of two teleworkers provided an impetus for reviewing processes. The majority of anticipated barriers were overcome easily by streamlining activities, using existing resources, and implementing new tools. Communication is enhanced through instant messaging and daily team meetings. Limitations posed by the employer provided hardware are still under consideration. Currently, BGL is supported by a team of four GCs, with two working onsite and two remotely. Advance planning provided a smooth transition for incorporating teleworkers and continued evaluation contributes to ongoing success. Team structure is similar to when all employees were onsite with GCs contributing to daily activities and enjoying task and project diversity.

Effectiveness of Telephone Genetic Counseling for Parkinson Disease and Association with Disease Status and Genotype

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Introduction: While numerous studies have demonstrated the effectiveness of telephone genetic counseling, there is currently a lack of published data regarding its use in counseling for complex disorders and the potential associations between knowledge retention and patient characteristics. This study evaluated the effectiveness of telephone genetic counseling for Parkinson disease (PD) in individuals tested for the *LRRK2* G2019S gene mutation, which is associated with a 30 % risk of developing PD by age 80. Methods: After testing, telephone genetic counseling was performed by a single genetic counselor. Following the counseling session, participants were asked to complete an online survey that assessed their understanding of the information provided during the session. Knowledge retention was compared between study groups defined by PD status (affected vs. unaffected) and LRRK2 test results. Results: Of 653 eligible participants, 359 completed the survey (55.0 %). The average number of correct responses was 9.5 out of 11 (86.4 %), with no significant difference among study groups. However, when questions were analyzed individually, significant group differences were detected. LRRK2 carriers were more likely to respond correctly to a question regarding segregation of the LRRK2 mutation (>=90.0 % vs. <=61.4 % in LRRK2-negative; p=0.001), while *LRRK2*-negative individuals were more likely to respond correctly to 2 questions regarding the risk of PD in a non-carrier (>=89.1 % vs. <=75.0 %, p=0.003; >=91.2 % vs. <=86.7 %, p=0.03). When asked about PD risk and aging, individuals with PD were more likely to respond correctly than unaffected subjects, regardless of genotype (>=95.9 % versus <=79.2 %; p=0.005). Conclusions: This study demonstrates the effectiveness of telephone genetic counseling for a complex disorder and suggests that the specific information retained may correlate with an individual's disease status and gene test results. These findings may have implications for the use of telephone genetic counseling in patients with PD or other multifactorial conditions.

Systematic Processes to Formalize and Optimize Patient Engagement in a Large Healthcare System

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1. Geisinger Health System

Since the early 2000s, initiatives organized under two related concepts have sought to alter the landscape of health care delivery and health care research: (1) patient-centered care is a philosophy and a practice that privilege the perspectives, needs, values, and preferences of patients in everything from the design of hospital units to models of decision making and (2) in the domain of research and discovery, patient engagement entails similar strategies and aims,

with the overall goal of optimizing the outcomes and translation of a range of activities, from quality improvement to clinical trials. In early 2014, research leadership at the Geisinger Health System launched a revision of the system's research strategic plan with the recognition that the voice of patients in planning and executing research was non-existent. In response, the revised strategic plan included recommendations to make patient engagement the "default" – rather than the exception – in Geisinger research and discovery and to establish mechanisms for achieving this goal. Those mechanisms include the establishment of a standing patient and family engagement working group with specified tasks and timeframes and the development of a conceptual framework for patient and family engagement to guide investigators in their efforts to enlist participants in the design and conduct of research, especially research involving definitions and measures of patient outcomes. We will present the strategies developed by the Geisinger working group and share materials employed to encourage measurable patient engagement in all aspects and phases of research and discovery. We will discuss the role played by genetic counselors in the Geisinger working group and suggest roles for broad professional investment in promoting patient engagement strategies.

Certified Genetic Counselors in Japan: Current Status 2014

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Introduction: We report the current status of certified genetic counselors in Japan. The Japanese certification program for genetic counselors began in 2005. In this program, a certified genetic counselor is described as "an expert that assists clients suffering from genetic problems in conjunction with clinical genetic specialists and protects their rights to facilitate the provision of high-quality clinical genetic medical care." The Japanese Association of Certified Genetic Counselors conducted this survey of their members. In Japan, all of the certified genetic counselors belong to this association. Materials and Methods: The subjects were 161 certified genetic counselors in Japan. This survey was carried out using a self-administered anonymous questionnaire (for confirmation of the responses, we requested them to write their names if they did not mind). The questionnaire was distributed by attaching it to emails to the certified genetic counselors in our mailing list, or postal mail delivery, and collected by email or postal mail delivery. The questionnaire contains 20 questions regarding their basic attributes and statuses (e.g., work situation, specialty, work details, and income) before and acquiring their certification as a genetic counselor, as well as any issues that they may have currently. Results: One hundred and twenty subjects responded (response rate: 72 %). All of the respondents were employed after acquiring their certification. Over 90 % of the certified genetic counselors were female. Their ages widely ranged from twenties to fifties. Medical institutions accounted for the highest percentage as work places, where they belong to various specialty departments. Many of them felt that there are problems in their employment conditions. More than half of them have participated in a seminar required for continuation of their qualification during their vacation time. Following more detailed analyses, we will report the current status of certified genetic counselors in Japan.

Genetic Test Utilization Review: Moving it Upstream

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1. Mayo Clinic

Many large healthcare organizations have instituted genetic test utilization management (UM) programs to help address the growing number and cost of genetic tests ordered, which due to the complexity and large array of available testing options, are particularly prone to errors. Mayo Clinic implemented a UM program for review of sendout genetic testing that is connected to its large referral catalog through Mayo Medical Laboratories (MML). In the initial phase of this UM program, test orders were reviewed by a genetic counselor team for potential errors and appropriateness of testing at the point of sendout through the MML Referrals department. This included a review of the medical record, test paperwork, and whether or not the test was currently in the MML referral catalog. The second phase of the program centered upon genetic sendout tests for which DNA extraction/cryopreservation services were performed by the Mayo Clinic Molecular Genetics Laboratory. Test requests were reviewed after insurance preauthorization was obtained but before the specimen and test request were forwarded to the MML Referrals team. The UM program then evolved to move the review process upstream, closer to the time of order entry. The Mayo Clinic Department of Medical Genetics collaborated with the genetic counselor UM team to review sendout genetic test orders on the day of order entry, prior to the initiation of insurance review and precertification. A review of the data from the different phases of the genetic sendout UM program at Mayo Clinic demonstrate that by moving the review process upstream, resources of both time and dollars are conserved. Other benefits include redundancy reductions, increased discussions with ordering providers closer to the time the patient was seen, and education regarding testing trends and preferred referral laboratories.

XI. Professional Issues/Professional Roles

Genetic Counselor Workforce Issues: A Survey of Genetic Counselors Licensed in the State of Indiana

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We have observed the movement of genetic counselors (GCs) out of clinical positions in the state of Indiana. The aim of this study is to identify reasons for this movement and factors that might help employers retain board-certified GCs in clinical positions. Although there are some publications on access to GCs, the changing landscape of genetic services, and professional satisfaction among GCs, no studies have addressed this apparent recent shift away from clinical roles or why GCs change jobs. Methods: An anonymous on-line survey of GCs ever licensed in the state of Indiana was conducted. Subjects were recruited from the Indiana Network of Genetic Counselors (n=48) and the Indiana Professional Licensing Agency (n=85); invitees were encouraged to forward the invitation to previous co-workers. Results: There were 42 responses from GCs, most of who reside and are actively licensed in Indiana. Of these, 29 % reported they work for a laboratory or in industry and 71 % for a hospital. Thirty-seven percent of respondents reported working in their current position for less than 1 year and 26 % reported thinking about leaving their current position at least monthly. Of the 17 GCs (40 %) who reported changing jobs within the past 2 years, 94 % were previously working in a hospital clinic setting and 53 % reported currently working in a laboratory or industry position. Salary and flexibility were

most often reported as reasons for changing jobs. Additional analysis to identify factors associated with dissatisfaction and free-text comments will be analyzed for common themes. Conclusions: This is the first documentation of the movement of GCs out of clinical roles into industry positions. This changing landscape may impact the access to clinical services and the training of genetic counseling students. This data will provide employers with data to help attract and retain GCs in clinical roles.

What do Genetic Counselors who Work at Fetal Centers do?

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Introduction: When a fetal abnormality is suspected in pregnancy, referral to a multidisciplinary Fetal Center is evolving to be the standard of care. The roles and responsibilities of genetic counselors (GCs) in this setting has not been characterized. Purpose: The purpose of this study was to assess the roles and responsibilities of genetic counselors in Fetal Centers. All GCs working in a Fetal Center were eligible. GCs were identified by two separate methods. 1) GCs had previously been ascertained by a demographic survey about Fetal Centers and were emailed directly. 2) GCs were recruited to participate on the NSGC Prenatal Special Interest Group (SIG) message board. Methods: An online survey was created and administered via REDCap, a secure web application for building and managing online surveys and databases. Questions were compiled from a review of the literature on defining GCs roles. Survey responses were tabulated using descriptive statistics. Results: From January to March of 2015, 68 GCs completed the survey. Of the GCs who were emailed, 54 % participated. One-fifth of respondents were recruited from the NSGC SIG post. GCs from 24 states were represented and demographics were comparable to the NSGC membership. All respondents indicated that they provided direct patient care, ordered tests and managed results. The majority of GCs also obtain insurance authorizations (88 %), provide case management (79 %), and perform administrative tasks like scheduling (71 %). While GCs were involve with teaching (63 %) and research (22 %), their average effort was less than 10 % for these tasks. Direct patient care required >50 % of the GCs' effort on average. Conclusions: Genetic counselors' skills in patient care and expertise in genetic testing are utilized in the Fetal Center setting. These skills are core competencies for GCs. New graduates from genetic counseling programs or GCs looking for a new opportunity should pursue or create a Fetal Center position.

Comparing Pharmacy and Genetic Counseling: Education Related to Pharmacogenomics and Attitudes about Roles and Collaboration in Clinical Pharmacogenomics

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Background: Genetic counselors (GC's) and pharmacists have been proposed as an ideal team to help provide clinical pharmacogenomic services. Due to this topic's limited research, this study sought to assess their interest in collaborating, level of preparedness to discuss pharmacogenomics, and barriers to professional involvement and roles in clinical implementation. Methods: Third/fourth year pharmacy students, second year GC students, and recent GC alumni from fifteen universities with coexisting pharmacy and GC programs were sent an email invitation to participate in an online survey. The survey was developed by the primary investigator, piloted on GC students, and revised based on feedback.
Results: 103 individuals responded to the survey. The majority were interested in collaborating with either a pharmacist (n=75, 80.6 %) or a genetic counselor (n=72, 84.7 %), and saw a role for both professions (n=94/96) in clinical pharmacogenomics. Participants did not feel adequately prepared to speak to physicians or patients about pharmacogenomic information and indicated a need for further training. GC alumni were more likely to agree, than other participant groups, that the following acted as barriers to becoming involved in clinical pharmacogenomics: their role in clinical pharmacogenomics is uncertain (p=0.001), and their lack of personal interest is a barrier to their involvement (p=0.011). While most participants elected pharmacogenomic roles that would traditionally align with their profession, there was some overlap of anticipated roles between professions. Discussion: While respondents expressed interest in collaborating and saw a role for both professions, most did not feel adequately prepared to discuss pharmacogenomics. This suggests a need for additional pharmacogenomics education during training and continuing education. Since GC alumni perceived more barriers to becoming involved in clinical pharmacogenomics, we suggest collaborative efforts begin at the student level.

The Evolving Partnership Between the Clinical and Laboratory Genetic Counselor

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Opportunities for and responsibilities of laboratory genetic counselors (GC) are evolving. This ongoing growth has an impact on the traditional scope of the clinical genetic counselors' role. In this report, we present the evolution of both roles at Seattle Children's Hospital and the division of responsibility at each step of the genetics evaluation. Historically, the clinical genetic counselor has been involved in all aspects of the patient's pediatric genetic testing experience, including intake, evaluation, test selection, pre- and post-test counseling, and test coordination. With the rapid expansion of test options, the addition of the lab GC's expertise regarding genetic testing methodologies provides positive support to the clinical GC in the effort to select the most appropriate test for each patient. The laboratory GC can more efficiently recommend reference laboratories based on internal lab-defined variables such as institutional contracts, reducing the rework of order triage. The lab GC also has a unique window into institution-wide practices and in consultation with the clinical GC can partner to direct patient referral to genetics clinic when non-genetics specialists request guidance for genetic test orders. The authors highlight the opportunities for a collaborative and supportive relationship of the lab and clinical GC and their contribution to the successful implementation of genetic services. This partnership results in improved patient care and genetic counselor satisfaction.

Psychiatry/Neurology

The Changing Age of Individuals Seeking Presymptomatic Genetic Testing for Huntington Disease

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Huntington disease (HD) is a progressive neurological disorder with onset typically later in life. Presymptomatic genetic testing is available for at-risk individuals to clarify their HD status. By defining the characteristics and motivations of individuals who seek presymptomatic genetic testing for HD, genetic counselors can provide comprehensive and personalized care. The aims of this study were to: 1) determine whether or not the average age when individuals seek presymptomatic genetic testing for HD has decreased over time, 2) define motivations for seeking testing and correlate them with age at testing, and 3) explore genetic counselors' perceptions of the shift in age. A small but statistically significant decrease in age was observed (p=0.045). The relationship between age at testing and year of testing is modified by whether or not an individual was in a committed relationship at the time of testing (p=0.03). A survey of individuals at risk for HD was also administered to elucidate the most frequently cited motivations for testing and correlate them with age at testing. Three motivations showed a significant correlation with age at testing; individuals who were tested at younger ages were significantly more likely to cite "To learn whether or not you would develop HD" and "To make choices about further education or a career" (p<0.05). "To give children a better idea of their risk" was more frequently cited as a motivation for testing by older individuals (p<0.002). Finally, a survey was given to genetic counselors to determine their perception of a change in age. Sixteen percent of genetic counselors surveyed perceived a change in age of testing. All of these respondents felt the age at testing has decreased, and have provided presymptomatic testing for ten or more years. The findings from this study can be used by genetic counselors to help provide more personalized counseling based on the age of the individual seeking testing, and provide a starting point for more research into the relationship between age at testing and motivations for testing.

Detection of Causative Variants Using Multigene Panels in a Pediatric Population with Epilepsy

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Guidelines for ordering genetic testing for epilepsy have not been developed and there is little information available on the yield of multigene panels for epilepsy. The purpose of this study was to determine the yield of epilepsy multigene panels among a pediatric population, as well as to identify potential clinical predictors of obtaining a causative genetic variant using epilepsy multigene panels. This retrospective medical record review examined the data of 117 pediatric epilepsy patients at a large tertiary referral center who had at least one epilepsy multigene panel of any type ordered between January 1st, 2009 and December 31st, 2013. The association of clinical predictors with causative results was analyzed using the chi-square test, Fisher's exact test, and Wilcoxon rank-sum test. Of 124 epilepsy panels ordered, 17 (14 %) received a causative result. Tonic or atonic seizures detected on EEG were significantly associated with causative results (p=0.04). A higher proportion of children with myoclonic seizures on EEG had a causative variant identified (p=0.06). Microcephaly, age of onset of epilepsy, developmental delay, drug resistant epilepsy, and abnormal brain MRI results were not significant. There was no significant relationship between number of genes on multigene panels and panel results. This is the largest study examining yield and clinical characteristics of patients with causative variants from epilepsy multigene panels. The overall yield in a pediatric population was comparable to other studies. This study identified that certain seizure types (tonic or atonic seizures on EEG) are clinical predictors of causative multigene panel results, however further studies are needed to confirm these clinical predictors and clarify the utility of various ordering practices for genetic testing in epilepsy.

Complexities of Genetic Counseling for Amyotrophic Lateral Sclerosis: A Case of Two Distinct Mutations in a Single Patient

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Amyotrophic lateral sclerosis (ALS) is a degenerative disease of the motor neurons occurring in ~2 per 100,000 individuals. The disease is progressive leading to limb paralysis and death from respiratory failure with 2–4 years median survival. In ~10 % of ALS cases, the disease is inherited in an autosomal dominant pattern (AD-ALS) and penetrance is age-dependent. Approximately two-thirds of AD-ALS can be explained by mutations in any one of four genes: *C9orf72, SOD1, TARDBP*, and *FUS*. However, mutations in several other genes have also been associated with AD-ALS including *ANG, OPTN*, and *VCP*.
We report the identification of two disease-causing mutations in the SOD1 and ANG genes in an individual with AD-ALS. Onset of symptoms was at 60 years with weakness in the right upper limb. Cognition was normal. The patient's ancestry was Irish and Scottish. Disease progressed rapidly with death occurring 2 years after diagnosis. The patient's mother and maternal grandfather also had ALS. Genetic testing identified an I113T missense mutation in the SOD1 gene and a K41I missense mutation in the ANG gene. Mutations in *SOD1* are associated with AD-ALS and the penetrance of the I113T mutation is reported to be reduced. Missense mutations of the ANG gene have been associated with ALS in the British Isle populations. The K41I mutation is rare and predicted to be deleterious. The patient's parents were not available for testing so from which parent(s) each mutation was inherited could not be determined. It is unclear to what extent either or both mutations contributed to disease in this case but both are likely contributing. *ANG* mutations are more common in this patient's ancestry and consistent with rapid disease progression. However, recurrence risk counseling for her offspring is complicated as either mutation can cause AD-ALS albeit with varying penetrance and expressivity.

An Investigation of Neurologists' Perceptions of the Value of Genetic Counselors in the Neurology Clinic

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Introduction: Genetic counseling outcomes research focuses on the impact of clinical genetic counseling services on patient care. Measuring genetic counseling outcomes involves examining the roles genetic counselors play, the value added by their services, and the resulting patient outcomes. Other healthcare professionals who work in close association with genetic counselors are in ideal positions to provide one perspective on the value of genetic counselors. The purpose of this qualitative study was to assess perceptions of genetic counselors' roles, value added, and resulting patient outcomes from the perspective of neurologists. Methods: Clinical neurologists or neurogeneticists currently working in the United States with genetic counselors were recruited through emails to 56 genetic counselors that indicated a specialty in neurology on the NSGC website. Of the 42 identified neurologists, 10 from various U.S. regions participated in semi-structured audio-recorded phone interviews and 7 rated the value of specific genetic counselor duties. Inductive and cross case analysis methods yielded several prevalent themes. Results: Neurologists indicated genetic counselors' most valuable contributions are genetic expertise and specialized training, especially in genetic

testing. They unanimously agreed that genetic counselors are very valuable to their neurology practice in terms of explaining genetic etiology and risk to patients, facilitating the genetic testing process, and providing psychosocial support and resources to patients. They also indicated genetic counselors have an important role in clinic coordination. Barriers to genetic counselors included lack of funding and limited availability. Discussion: This study indirectly measured genetic counseling outcomes through the eyes of their physician counterparts in the neurology setting. The results characterize valued roles for clinical genetic counselors in a multidisciplinary team, identify their unique contributions to patient care, and support the importance of their contributions to patient outcomes.

Perceptions and Utilization of Genetic Counseling by Adults with Charcot-Marie-Tooth

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Background: Charcot-Marie-Tooth disease (CMT) is a hereditary motor and sensory neuropathy affecting one in 2,500 people globally. Objective: The purpose of this study was to assess the perceptions, experiences, and utilization of genetic counseling services by adults with CMT. Methods: Data was collected using an online anonymous survey distributed through the Hereditary Neuropathy Foundation Results: The survey had 724 total respondents, not all of whom answered every question. Overall, 49 % of participants had received genetic counseling, from a neurologist (54 %), genetic counselor or medical geneticist (37 %) or other provider (9 %). Of 236 respondents, 72.4 % (186) indicated they had never been offered an appointment with a genetic counselor. Of 535 respondents , 51.4 % (275) indicated that they would be interested in being referred to a genetic counselor. Participants who have not had genetic counseling (N=186) were more likely to identify receiving support as a potential benefit of this service than those who had genetic counseling. They were also more likely to be concerned about potential negatives such as discrimination and cost, compared to those who had genetic counseling. Of 652 respondents, 52.6 % indicated that they had been offered genetic testing, 79.6 % chose to pursue this service, and 92.5 % of those that received testing were happy with their decision. Of those who were not offered or did not pursue testing, 71.6 % (227) indicated they were interested in pursuing genetic testing. Discussion: The results of this study suggest that many people with CMT are not being referred for genetic counseling and testing. Genetic counselors can work to eliminate this barrier by educating neurologists about benefits of pre and posttest genetic counseling for CMT patients. Genetic counselors should also consider spending more time focusing on support needs for these patients, as it is highly desired in this population.

Planning, Implementation, and Evaluation of a New Clinical Simulation: Psychiatric Disease Case

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Psychiatric illnesses are common and have complex etiologies with genetic and environmental factors. Despite the fact that genetic counseling can benefit individuals and family members affected by psychiatric illness, genetic counselors often feel unprepared or unqualified to address these conditions. Training opportunities to address the needs of individuals with a psychiatric illness are limited in the clinical setting since few patients are seen by genetic counselors for the primary indication of psychiatric illness. However, many of the patients seen by genetic counselors are affected by some form of psychiatric disorder, either as part of a larger genetic diagnosis or as an isolated issue. Without deliberate training, genetic counselors may continue to feel unprepared and patient's needs may continue to be unmet. To introduce more psychiatric illness content into genetic counseling clinical training, a clinical simulation was developed, implemented, and evaluated at the University of Alabama at Birmingham (UAB) Genetic Counseling program. The simulation scenario lasted 90 minutes, including pre and post briefing and evaluation. The scenario required genetic counseling students (n=11) to address disease etiology and recurrence risk with a standardized patient with bipolar disorder. Participation was required by the UAB curriculum, but all students consented to their data being used for research purposes. Participants' responses were evaluated to determine if the simulation experience increased their content knowledge and their comfort with providing genetic counseling for this indication. Pre and post simulation, students used a five-point Likert scale to self-rate their comfort level with providing psychiatric genetic counseling. Content knowledge was measured by open responses to questions concerning specific vignettes. While content knowledge showed no change post-simulation, comfort level increased by 65.9 %. Our findings suggest that the simulation could potentially encourage students to engage with an underserved population.

Exploring Physician Perceptions of Psychiatric Genetic Counseling and Conceptual Barriers to Referrals

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Background: The world's first specialist psychiatric genetic counseling (PGC) service of its kind was founded in Vancouver in 2012, and the discipline is emerging as a specialty within the genetic counseling profession. While clear benefits of PGC services have been demonstrated, experience in Vancouver reveals that many physicians do not regularly refer to the clinic. Understanding the barriers that obstruct physicians from making referrals to PGC will allow the development of mitigating strategies. Methods: Using a grounded theory approach, telephone interviews were conducted with 12 physicians from Vancouver who were aware of a local PGC clinic with the aim to understand the process by which physicians make decisions about referring patients for PGC. Interviews were recorded, transcribed verbatim, coded, and a constant comparative analysis of emergent themes was conducted. Results: Patient cues and physicians' perceptions about the purpose of PGC inform their referral practices. Physicians perceive PGC to be an information-focused intervention, and consider referral when patients express desire for information about recurrence risk or etiology that they feel unable to address themselves. Even when physicians are able to identify the psychotherapeutic benefits of PGC, patient psychotherapeutic needs are not perceived as cues for referral to PGC. Implications: These data suggest that further work is necessary to position PGC in physicians' minds as a service that could potentially benefit most individuals with psychiatric disorders and their families. In particular, it will be important to increase physicians' awareness of: a) the importance of psychotherapeutically-oriented counseling around issues of risk and etiology, and b) the role that genetic counselors can play in this domain, in a manner that is complementary to and supportive of the role of the physician.

Compound Heterozygosity of Two *MECP2* Deletions with Paternal Inheritance of a Late-Truncating Mutation in a Female with Atypical Rett Syndrome

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Introduction: Rett syndrome (RS) is an X-linked dominant neurodevelopmental disorder caused by mutations in *MECP2* that predominantly affects females. RS is characterized by a period of apparently normal development until 6–18 months of age, followed by gradual loss of motor and communication skills. The majority of cases are sporadic, with only a few maternally-inherited mutations described. Rarely, males with RS due to a mosaic point mutation or hemizygosity for a late-truncating mutation have been described. Purpose: To expand the current knowledge of familial Rett syndrome, we describe a case of a paternally-inherited late-truncating mutation and a maternally-inherited variant of unknown significance (VUS) in *MECP2* in a female with atypical RS. Methods: Next generation sequencing of a 51-gene panel for epilepsy was completed and two *MECP2* variants were identified in the proband. Confirmations and subsequent parental testing were performed by Sanger sequencing. Results: We identified two novel deletions in exon 4. A maternally-inherited deletion of 2 amino acids (c.1101_1106delCCACCA) and a paternally-inherited deletion of 70 nucleotides (c.1129_1198del70) resulting in late protein truncation. In-frame deletions within this region of exon 4 have been described previously and are considered of unclear clinical significance. The paternal frameshift mutation is likely pathogenic, consistent with rare reports of late-truncating mutations in affected males and carrier mothers. Conclusions: Here we report a case of a female with atypical RS who inherited a late-truncating mutation from her symptomatic father and a VUS from her mother with learning disabilities. Males with late truncating mutations similar to the c.1129_1198del70 mutation have been described with intellectual disability and atypical RS. This family represents the first report of paternal transmission of one of these variants. It is unclear if the more severe phenotype of the proband reflects the phenotypic variability of late-truncating mutations and/or can be attributed to the maternal VUS.

Training to Provide Psychiatric Genetic Counseling: How does it Impact Recent Graduates' and Current Students' Attitudes Towards Individuals with Psychiatric Illness and Their Readiness to Provide Genetic Counseling for this Population?

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Background: Mental illness (MI) is pervasive in the general population and genetic counselors (GCs) frequently see patients with MI as either a primary indication or incidentally. GCs report discomfort in providing psychiatric genetic counseling (PGC), suggesting the need for a critical look at current training in this area. This study aimed to investigate PGC training and its impact on perceived preparedness to provide PGC (preparedness). Methods: Current students and recent graduates (graduation year 2009–2014) were eligible to complete an anonymous survey, sent via the NSGC listserv between Oct-Nov 2014. The survey included demographic questions and questions characterizing PGC training and outcomes (open- and closed-ended). Bivariate correlations ($p<.10$) identified variables for inclusion in a logistic regression model to predict preparedness. Data were checked for assumptions underlying logistic regression. Results: Of 1,167 eligible NSGC members, 286 completed the survey (response rate: 24.5 %; 33.9 % students, 46.8 % with a personal history of MI). The logistic regression model χ^2 (8)=84.87, $p<.001$) explained between 37.1 % (Cox & Snell R^2) and 49.7 % (Nagelkerke R^2) of the variance in preparedness scores. More frequent PGC instruction (OR=5.13), more active methods for practicing risk assessment (OR=4.43), and education on providing resources for MI (OR=4.99) made uniquely significant contributions to the model ($p<.001$). Responses to open-ended questions revealed an overwhelming interest in further PGC training, particularly enabling 'hands on' experience, and the sentiment that current PGC training is inadequate. Discussion: This exploratory study suggests that enriching PGC training by offering more frequent instruction on PGC and more active opportunities to practice PGC skills will support students in feeling more prepared to provide PGC after graduation. GC training programs are in an ideal position to improve outcomes for future students by evaluating their current approach to PGC training and exploring new interventions designed to improve preparedness.

Perspectives on Genetics Among Individuals with Trichotillomania

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An estimated 3.7 million people in the United States struggle with Trichotillomania (TTM), a psychiatric disorder involving chronic or compulsive hair-pulling, leading to excessive hair loss frequently involving pronounced functional impairment, and often associated with depression, anxiety, low self-esteem and impaired quality of life. TTM twin and family studies indicate that genetic factors contribute significantly, with heritability of 76 % and recurrence rates among first-degree relatives of approximately 11 %. Inheritance of TTM is likely to be complex and no molecular testing is available currently. The purpose of this study was to explore beliefs, experiences and attitudes of individuals with TTM about the potential roles of: 1) heritability in causation, 2) genetic testing, and 3) genetic counseling in this disorder. We recruited individuals with a self-reported history of TTM through online TTM support groups to participate in an online, anonymous survey consisting of 40 multiple choice and open-ended questions. Among the 299 respondents who completed the survey, 31 % reported having a first-degree relative who also has TTM. Approximately one-third (35 %) indicated that they were uncertain of the recurrence risk of TTM, 29 % believed there was an up to 50 % chance of recurrence, and the remaining 37 % believed there was less than a 25 % chance of having a child with TTM. Many (63 %) were interested in hypothetical genetic testing for TTM and 43 % indicated interest in genetic counseling. While 48 % did not see direct benefits to receiving genetic counseling others saw pursuing genetic testing as a public education benefit. Only 7 participants reported meeting with a genetic counselor, with two reporting the meeting as unhelpful. Our findings suggest the recurrence risk for TTM may be higher than previously estimated. They also highlight variable interest in and understanding of genetic testing and counseling.

Novel In-Frame Deletion in *GRIA3*: A Case Report

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X-linked intellectual disability (XLID) is a collection of genetically heterogeneous disorders thought to explain approximately 16 % of all intellectual disability in males. More than 90 genes on the X chromosome

have been implicated in XLID thus far. One such gene, *GRIA3*, encodes glutamate receptor 3, and is located on chromosome Xq25. Although clinical and functional data on *GRIA3* in the literature is limited, several reports have shown mutations in *GRIA3* to be associated with varying degrees of intellectual disability, behavioral problems, autistic features, seizures, poor muscle bulk, short stature, and dysmorphic features. Here, we present a novel *GRIA3* in-frame deletion located in a functional domain of coding exon 13 (c.2167_2175delGCCCGAGTG), which was identified in a male proband with severe intellectual disability, behavior problems, hypothyroidism, and dysmorphic features. The variant was shown to segregate with disease in all affected male members of this individual's family, allowing the alteration to be reclassified from a variant of uncertain significance to a variant that is likely to be pathogenic. Previous testing in this proband and his family members detected two translocations [t(4q;10p) and t(6;9)] that did not segregate with disease in the family. The data presented here not only contributes additional phenotypic information regarding *GRIA3* alterations to the currently limited literature, but also highlights the importance of family studies in variant reclassification efforts.

An Extension of our Assessment: Addressing Psychiatric Concerns in Prenatal Genetic Counseling

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There is a broad range of psychiatric disorders that can present within the prenatal setting, including depression and anxiety. The relative high frequency of mental health disorders in pregnancy and the potential for adverse outcomes indicates that there would be benefit in identifying a history of mental health disorders during pregnancy so that appropriate referrals can be made. This study was designed to determine if any specific demographic or historical factors could be correlated with depression and anxiety among patients being seen for prenatal genetic counseling. Prior to seeing the GC, participants were given an anonymous 32-question survey which assessed demographics, pregnancy history, genetic counseling referral indication, mental health history, and two 8-question PROMIS screens: one for depression, and one for anxiety. In total, 122 women participated in the study. Overall 14.8 % of participants screened positive for depression and 24.6 % of participants screened positive for anxiety. We were able to determine 7 factors which correlated with current depression status along with 7 factors which correlated with anxiety status. The only two factors which were statistically significant for both a positive depression and anxiety screen were the historical questions assessing if there was a personal history of a mental health disorder. This study supports the idea that a mental health history assessment is an extension of the risk assessment which is already performed within the prenatal counseling session. We believe GCs have the proper counseling and risk assessment skills to be particularly useful identifying these patients. As the roles of genetic counselors expand, we recognize that mental health disorders will continue to be a part of genetic counseling sessions. With the information gleaned from this study, we have supported the idea that there is value to assessing mental health in pregnancy, and that GCs have a particularly unique opportunity to become part of an interdisciplinary team to better assess and assist our patients.

Next-Generation Panel Testing for Neuromuscular Disorders Gives a High Diagnostic Yield in a Clinic-Based Population

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The genetic diagnosis of neuromuscular disorders has long been a significant clinical challenge. The high genetic heterogeneity and phenotypic overlap between disorders make molecular confirmation laborious and expensive. Published diagnostic algorithms to guide genetic evaluation are complex, involve multiple testing steps, and may involve invasive procedures such as muscle biopsy. Patients and clinicians often elect to stop testing before a genetic diagnosis is acheived. The advent of next-generation sequencing (NGS) technology has reduced the price of DNA sequencing to such an extent that it is no longer necessary to priorize individual genes for testing. In the last year, several commerical NGS multigene panels for neuromuscular disorders have become available. The application of such panels has the potential to revolutionize the genetic diagnosis of patients with neuromuscular disorders.

We present our experience to date with the use of NGS multigene panel testing for neuromuscular disorders in a clinic-based population. Of 26 total NGS neuromuscular panels sent, 14 (53.8 %) were positive for a genetic diagnosis, 10 (38.5 %) reported variants of uncertain significance, and 2 (7.7 %) were negative. The positive diagnostic yield was found to vary widely depending on the specific test indication: genetic diagnosis was achieved in 7/12 (46 %) cases of limb-girdle muscular dystrophy, 6/7 (86 %) cases of non-dystrophic myotonia, 0/2 (0 %) cases of 'other myopathy', 0/3 cases of cramping/pain syndromes, and 1/2 cases of other neuromuscular disorders. The high frequency of variants of uncertain significance encountered in this testing complicated test interpretation and was frustrating to patients and clinicians. We will present our approach to variant interpretation and use specific case examples to illustrate both the power and limitations of this new technology.

Clinical Experiences with a *PCDH19*-Related Epilepsy Cohort

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Mutations in the PCDH19 gene cause *PCDH19*-Related Epilepsy, a relatively newly recognized disorder characterized by early-onset epilepsy, intellectual disability, developmental delay and autism spectrum disorder. *PCDH19* is located on Xp22.1, yet there appears to be a unique sex-limited pattern of expression in which girls manifest the phenotype while carrier males do not. Until recently, mutations had been documented as either *de novo* or transmitted from unaffected fathers to affected daughters. In the Epilepsy Genetics Program at Boston Children's Hospital, we follow 11 girls with variants in the PCDH19 gene, 4 of whom have atypical presentations that present diagnostic and counseling challenges. In this series, we report on cases in which predicted pathogenic variants have been transmitted from seemingly unaffected mothers to affected daughters. Since inheritance patterns are often utilized to assist in determining pathogenicity of novel variants, such findings complicate *PCDH19* variant interpretation. We also report on patients with *de novo*, predicted pathogenic variants whose features are not entirely consistent with the *PCDH19* phenotype. These scenarios present diagnostic challenges and may lead to variant misinterpretation by clinicians and families. Particularly concerning are situations in which variant re-analysis leads to re-classification. We report on one family of a girl with a *PCDH19* variant initially reported as likely-pathogenic, who started a support organization to fund research into *PCDH19*-Related Epilepsy. The laboratory later re-classified the variant as benign, thus leading to both retraction of the diagnosis for the patient and the loss of community identity for the family. Our cohort of females with *PCDH19* variants suggests that there is still much to be learned about both the phenotype and transmission pattern of this unusual X-linked condition. A *PCDH19*

patient registry and functional studies are currently underway to address these gaps in knowledge.

Yield of Clinical Genetic Testing for Amyotrophic Lateral Sclerosis-Associated Mutations in a Tertiary Care ALS Clinic

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The practice of genetic testing and genetic counseling for amyotrophic lateral sclerosis (ALS) has been transformed in recent years with the identification of novel genes including *C9orf72*, the recognition of the etiologic link between ALS and frontotemporal dementia (FTD), and the advent of next generation sequencing technology. Little information is available on the yield of genetic testing in clinic-based ALS populations. We report testing outcomes of our first year of a clinic-based ALS genetic testing program. ALS genetic testing was offered to patients with 1) familial ALS 2) a combined ALS/FTD phenotype 3) ALS with onset <50 years old 4) ALS who requested genetic testing and 5) asymptomatic family members at 50 % genetic risk. Twenty-nine (29) persons had genetic testing, including 27 ALS patients and 2 asymptomatic family members at 50 % risk. Six (6) ALS patients had *C9orf72* testing only and 21 had multigene panel testing. Genetic testing was positive in 7/27 (25.9 %) of ALS cases, negative in 15/27 (55.6 %) of ALS cases, and identified variants of uncertain significance in 5/27 (18.5 %) of ALS cases. Among patients with familial ALS, 7/11 (63.6 %) tested positive, 2/11 (18.2 %) were found to have a variant of uncertain significance on panel testing, and 2/11 (18.2 %) tested negative on panel testing. No patients in the other testing categories tested positive; one patient with an ALS/FTD phenotype was found to a have an intermediate *C9orf72* repeat expansion of uncertain significance. Of patients identified with mutations, 4/7 (57.1 %) had pathogenic expansions in *C9orf72*, and 1/7 had mutations each in *SOD1, FUS*, and *ERBB4*. Our early data concur with published literature reporting that ALS mutations are found in two-thirds of familial cases. We advocate offering *C9orf72* testing to all patients with ALS, with reflex to panel testing for patients with a positive family history.

Understanding Psychiatrists' Preceptions Surrounding Psychiatric Genetics and Genetic Counseling Services

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Background: Shortly after the first specialty psychiatric genetic counseling (PGC) service began in Vancouver, Canada in 2012, a private PGC practice launched in San Francisco, CA. Though clear benefits of PGC have been demonstrated, including increases in empowerment and self-efficacy among individuals with mental illness, the majority of psychiatrists were not referring patients to the private PGC practice in San Francisco. Until now, no literature has focused on psychiatrist perceptions of PGC services. Methods: Ten physicians recruited from a pool of 41 eligible psychiatrists in the San Francisco area participated in the study. A qualitative study was conducted involving semi-structured telephone interviews with the psychiatrists, in which their perceptions and beliefs regarding potential challenges and benefits of PGC services for individuals with mental illness were explored. Results: Analysis of interview transcripts revealed conceptual and practical barriers that obstructed psychiatrists from making referrals to the private practice PGC clinic, which were classified into themes related to: 1) perceptions of PGC as focused almost exclusively on discussing information related to genetics and recurrence risk; 2) effects of the relative absence of trusting relationships between psychiatrists and genetic counselors; and 3) the need for psychiatrist education to clear existing misperceptions surrounding PGC. Conclusion: The conceptual and practical barriers identified in this study that obstruct psychiatrists from making referrals to PGC services provide enlightening, novel information for development of mitigating strategies that could be used in the San Francisco practice. These results also inform referral generation strategies for other genetic counselors who may be interested in setting up similar private practices.

XII. Public Health

Public Opinion of Newborn Screening for Disorders with Various Treatment and Intervention Options

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Newborn screening (NBS) is a public health program that identifies newborns with rare genetic disorders for whom early intervention or treatment can be beneficial. As the ability to screen for new disorders through NBS expands, attention must be paid to the characteristics of these disorders and how the framing of treatability influences stakeholder perceptions of the benefits of screening. This study aimed to better understand public opinions of the benefits of screening for certain types of disorders and how key terminology might impact these opinions. 5,840 participants in the NUgene biobank population were electronically surveyed. For the aims of this study, we developed and assessed twelve vignettes that described a disorder and associated characteristics such as treatability, likelihood of improved outcome, and risks of intervention. For each vignette, we randomized the use of the terms treatment and intervention between subjects to describe potential care options for affected infants. We assessed participants' perceptions of the benefits of screening based upon disorder characteristics. 555 individuals responded (response rate of 9.5 %). Participant ratings of benefit and importance were not influenced by the use of the term treatment versus intervention. Participants were most likely to perceive benefit in testing for a disorder if a treatment or intervention offered a guaranteed improved outcome. Participants rated little benefit in testing for a disorder if the treatment or intervention was risky and promised only a minimal increase in lifespan. Females were more likely to perceive screening benefits, as were participants with a child with a chronic illness or disability (Mann–Whitney U test, $p<0.05$). While participants perceived benefit in screening for most disorders, nuances in inter-vignette ratings suggest that participants distinguished between disorder characteristics. These results are an important addition to NBS policy decision-making, as they demonstrate a lack of consensus about screening benefits in expanded disorder scenarios.

Development of Sickle Cell Trait Notification Process of Newborn Screening Results: A Community Needs Assessment

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In 1988, Minnesota's Newborn Screening (NBS) Program began screening for hemoglobinopathies (HGB). The primary purpose was to identify newborns with sickle cell disease (SCD), but the incidental finding of this methodology yields trait (SCT) status. No active method of notification regarding trait status occurs in Minnesota at this time which is inconsistent with current medical practices of full disclosure of results. In order to understand community perspectives and desires regarding notification of SCT status identified through NBS, the Minnesota Department of Health held focus groups within at-risk communities. Focus groups addressed the importance of parents understanding the trait status of newborns, possible process for notification, and qualities desired in a notification process. All participants expressed the importance of parent notification and how the current lack of notification fails to meet community expectations. Through focus groups, it became clear no single notification process would meet all individual preferences of parents; rather, a multifaceted approach would best meet community expectations. Participants articulated four key qualities important for parental acceptance of trait results, including: knowledge base of individual providing information, personal relationship, provision of support/resources, and timeliness of notification. Unexpectedly, participants felt the entity providing this communication does not need a medical degree, rather a depth of knowledge on this specific topic. Lastly, focus groups identified the importance for community-based support groups and organizational efforts to increase awareness and education of trait within the community. In summary, SCT notification should include the following: 1) a minimum standard notification consisting of an approach which is multifaceted, timely, and facilitated by individuals with a working knowledge of HGB and counseling theories; 2) provision of sufficient resources/support; and 3) continued efforts to increase culturally appropriate general awareness of SCT and NBS.

Effect of Newborn Screening Collection Methods on Concentration of Markers for Newborn Screened Disorders

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Objective: To evaluate if samples collected from cord blood have a higher false positive rate than samples collected from the traditional heel stick collection method during newborn screening. Methods: We sent out 10 surveys to Neonatal Intensive Care Unit (NICU) level III Nurse Managers working in Utah (UT). We used our survey results to identify which NICU facilities used cord blood in 2011 as compared to 2009. We then performed a retrospective, de-identified, cumulative statistical analysis of 18 amino acids and acylcarnitines. We used 95 % confidence Intervals to ascertain the differences in concentrations of analytes. For our analysis on Congenital Adrenal Hyperplasia (CAH) samples, we looked at the number of abnormal first- and second-tier CAH testing in UT, age of collection for all CAH samples, overall distribution of age of collection, and individual age of collection for each NICU. To evaluate if differences between the ages of collection for CAH samples were significant, we used an analysis of variance test. Results: Neonatal Intensive Care Unit 1 (NICU1) is the only facility to fully implement the use of cord blood in 2011. 95 % confidence interval revealed no significant differences among the 18 amino acids and acylcarnitines. Our CAH results revealed that NICU1 had the highest increase in false positive results from 3 in 2009 to 39 in 2011. Conclusions: Results from the study indicate that the cord blood collection method affects Congenital Adrenal Hyperplasia newborn screening results by resulting it a higher false positive rate. In contrast, cord blood does not seem to have the same impact on amino acids and acylcarnitines of samples collected at <1 day of age.

Who Utilizes Genetic Counseling After Direct-to-Consumer Genetic Testing?

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Introduction: Direct-to-consumer genetic testing (DTC-GT) results lead some consumers to seek genetic counseling (GC), but little is known about these consumers and why they seek services. Methods: We analyzed pre-test (baseline) and post-test (2-weeks and 6-months) data from a longitudinal survey of new 23andMe and Pathway Genomics customers. Chi-square and t-tests were used to evaluate differences between GC users and non-users, and logistic regression to assess predictors of GC use. Results: Of the 975 participants included in this analysis, 43 (4.4 %) sought GC after testing, with 390 (40 %) reporting they would have used GC had it been available. GC users were 65 % female, 93 % white, and 49 % college educated. GC users were significantly ($p<0.05$) more likely to be younger (38 vs 46 years), to report poor general health (16 vs 3.7 %), to report prior use of GC (37 vs 7 %) and to report prior genetic testing (30 vs 14 %). GC users were significantly more likely to seek DTC-GT for health reasons (83 vs 62 %), to report a positive family history of more conditions (7.7 vs 6.6), and to report perceived elevated risk for more conditions (4.3 vs 2.9) at baseline. After testing, GC users were significantly more likely to report uncertainty about their test results (41 vs 27 %) and to report an increase in mean disease risk perception compared to baseline (2.8 % increase vs 20 % decrease). Each of these variables remained significant predictors ($p<0.05$) in regression analyses except family history, prior genetic testing, and baseline perceived risk. Conclusions: DTC-GT consumers have high interest in GC, but low levels of post-test use of services. GC users differed from the broader population of DTC-GT consumers in terms of age, self-reported health, prior use of GC services, and reactions to test results. These insights can help GC providers better prepare for clinical discussions of DTC-GT results.

Stakeholder Views on Newborn Screening Using Whole Genome Analysis

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Due to advances in next-generation sequencing technology the human genome can now be analyzed more quickly and at lower costs, a trend likely to continue. With greater accessibility, opportunities to integrate genomic information into public health and clinical care will expand. One potential clinical application of whole genome analysis (WGA) is newborn screening (NBS). Although studies have explored genomic analysis in the context of direct-to-consumer testing, the translation of WGA into the NBS setting is not well understood. The purpose of this study was to examine key stakeholders' views, perspectives, and values regarding the potential expansion of NBS to include WGA. We conducted four focus groups in English (3) and Spanish (1) with socioeconomically and ethnically diverse pregnant women (n=30), and one focus group with parents of children with immunodeficiency disorders (n=8). To elicit preferences regarding return of results, we provided information about case examples of pharmacogenomics and adult disorders such as hereditary breast and ovarian cancer. Focus groups were transcribed (and translated) verbatim, and a grounded theory approach was used to analyze the data. Several themes emerged from the results, including: 1) preferences for discussion of NBS with a physician during the prenatal period (for

traditional or WGA NBS); 2) a struggle between sentiments of "knowledge is power" and "ignorance is bliss" resulting in differing opinions about what WGA results participants would like returned (all results, medically actionable, adult onset, or pharmacogenomics); 3) a desire to store WGA results for potential later use, with some reservations due to potential of privacy violations, and unwanted uses by researchers, the government or insurance companies; 4) preference for opt-in consent rather than opt-out for NBS if WGA is implemented. These results show that parents and pregnant women would like to be included in the NBS process, with implications for policy development should NBS be conducted with WGA.

Research Issues

Exploring the Process of Decision-Making About Participation in Genetic Research on Mental Illness

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Introduction: There are several barriers to recruitment for research on mental illness (MI), including distrust of researchers and social stigma. Among individuals who do participate in MI research, little is known about how and why they decide to participate. This study explored the process of decision-making around participation in genetic research on MI, including motivating factors and perceived benefits of participation, and expectations regarding return of genetic research results. Methods: This qualitative study utilized grounded theory methodology. Open-ended interviews were conducted with 16 individuals who had either completed participation or had recently made a decision about participation in a genetic research study on MI led by genetic counselors. Interviews were transcribed and analyzed using the constant comparative method and open, axial, and theoretical coding procedures. Results: Illness acceptance and establishment of trust with the research team and institution were foundational elements required for individuals to consider participating in genetic research on MI. Main motivators for participation included perceived personal relevance, anticipated benefits, a desire to "give back", and accessible study procedures. Perceived benefits of research participation included access to support and resources via the research team, the opportunity to learn, and improved self-worth. Return of personal genetic research results did not appear to be a major factor in the decision-making process regarding participation. Conclusion: Our data suggest that participation in genetic research on MI helps make meaning of individuals' illness experience and empowers them to adopt positive health management strategies. Our results support the value of genetic counselors in research. Genetic counselors possess a unique skill set that enables them to build trusting relationships that facilitate recruitment and retention of participants. These findings may inform strategies that improve participation rates, decrease attrition, and maximize participant benefits.

Expectations of False Reassurance in a Genetic Sequencing Cohort

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Absent, negative or uncertain genetic testing results may lead patients to be falsely reassured about their disease risks, which may affect their subsequent adherence to recommended screening practices. Studies of single gene and direct-to-consumer genetic testing have found that false reassurance occurs but does not lead to inaccurate risk perceptions or inappropriate screening. However, genetic sequencing differs from previous genetic testing in its breadth and potential for generating uncertain results, making it important to assess false reassurance in this context. This study was designed to determine the magnitude and correlates of expectations of false reassurance among 151 participants in a genome sequencing study. Participants completed a survey assessing their expectations of false reassurance and knowledge of genome sequencing. Survey respondents were 59 years old on average and the majority had a college degree or beyond (71 %). Roughly half of the participants were male (62 %) and non-Hispanic African Americans (49 %). Overall, only 17 % of respondents expected some false reassurance. Lower expectations of false reassurance were significantly correlated with less knowledge about genome sequencing (R=−0.3926, p<0.01) and having less than a college degree (X2 = 7.16, p=0.03). Our data suggest the importance of emphasizing the potential for false reassurance in sequencing during the consent process, particularly when counseling participants with less formal education. Further research is necessary to determine whether expectations of false reassurance affect downstream outcomes, such as adoption of recommended health behaviors, decisions to learn results from sequencing and satisfaction with study participation.

Returning Genomic Research Results to Biobank Participants

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1. Mayo Clinic

As highlighted by the recent announcement of the National Institutes of Health's Precision Medicine Initiative and the call for a 1 million participant national cohort, biobanks play an important role in genomic research to understand the biology of disease. Over time, biobanks store and curate information on participants and have the capacity to generate large amounts of genomic data. Some of these data may have important health implications for participants, raising the need to address return of results. Several recommendations have suggested researchers and biobanks have a minimum obligation to return research results that may be clinically actionable for participants. The Mayo Clinic Biobank is a large clinic-based biobank of 50,000 participants recruited irrespective of disease status and who provide health information and samples including blood and blood derivatives. As many participants continue to receive some, if not all, of their health care at Mayo Clinic, the Biobank has opted to return genomic research results that are: 1) analytically valid (test methodology is valid and can be replicated); 2) clinically valid (associated risks are established and substantial with high penetrance); and 3) clinically actionable (established therapeutic or preventive interventions or other actions that may change the clinical course of the disease are available). We will review our process for determining which genomic research results meet the criteria listed above. Additionally, we will describe how genetic counselors have been utilized to return genomic research results to biobank participants. Our experiences add a tangible example of how a large, non-disease-focused biobank manages research results, which may be useful for other researchers and biobanks as they develop policies. As biobank research continues to expand, it is important for genetic counselors to contribute to these conversations about which results are returned, how to implement the return, and how to facilitate necessary clinical follow up of genomic results generated in a biobank setting.