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NEXT GENERATION GENETIC COUNSELING

Traditional Roles in a Non-Traditional Setting: Genetic Counseling in Precision Oncology

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Abstract Next generation sequencing technology is increasingly utilized in oncology with the goal of targeting therapeutics to improve response and reduce side effects. Interpretation of tumor mutations requires sequencing of paired germline DNA, raising questions about incidental germline findings. We describe our experiences as part of a research team implementing a protocol for whole genome sequencing (WGS) of tumors and paired germline DNA known as the Michigan Oncology Sequencing project (MI-ONCOSEQ) that includes options for receiving incidental germline findings. Genetic counselors (GCs) discuss options for return of results with patients during the informed consent process and document family histories. GCs also review germline findings and actively participate in the multi-disciplinary Precision Medicine Tumor Board (PMTB), providing clinical context for interpretation of germline results and making recommendations about disclosure of germline findings. GCs have encountered ethical and counseling challenges with participants, described here. Although GCs have not been traditionally involved in molecular testing of tumors, our experiences with MI-ONCOSEQ demonstrate that GCs have important applicable skills to contribute to multi-disciplinary care teams implementing precision oncology. Broader use of WGS in oncology treatment decision making and American College of Medical Genetics and Genomics (ACMG) recommendations for active interrogation of germline tissue in tumor-normal dyads suggests that GCs will have future opportunities in this area outside of research settings.

Keywords Genetic counseling · Whole genome sequencing · Precision oncology

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Background

Advances in tumor biology and cancer genomics have led to a new era in cancer diagnosis and treatment, with identification of somatic mutations within tumors leading to greater potential for targeted treatment based on genomic mutational profiles. This approach is not entirely novel but has historically involved testing for specific somatic mutations dictated by cancer location or pathology (Dancey et al. 2012) . Increasing availability and decreasing costs of next generation sequencing technology are expanding the potential for widespread use of whole genome sequencing (WGS) of tumors as opposed to targeted mutational testing or panel testing.

Genome wide mutational analysis of tumor tissue requires parallel investigation of germline DNA in order to identify tumor specific mutations. Identification of germline mutations is secondary to the main purpose of this testing, generating discussion and debate about how results of parallel germline analysis should be addressed. The recently released American College of Medical Genetics and Genomics (ACMG) recommendations outline a minimum gene list for active interrogation and disclosure when clinical sequencing occurs on germline DNA, including the normal sample of a tumor-normal sequenced dyad (Green et al. 2013). Clinical genetic counselors (GCs) have not traditionally been involved in the process of somatic tumor analysis, but reports of actionable secondary germline findings within cancer predisposition genes (Johnston et al. 2012), in addition to the ACMG recommendations, suggest a role for the clinical cancer GC.

The Michigan Oncology Sequencing Project (MI-ONCOSEQ) is one initiative utilizing WGS to identify somatic mutations in tumors in an attempt to develop biomarker driven personalized oncology care. The project began in 2011 and was funded by the National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) as a Clinical Sequencing Exploratory Research (CSER) project in

July 2013 to study the challenges of utilizing genomic sequence data in routine clinical care. As one of three CSER sites studying targeted oncology, MI-ONCOSEQ began with the following goals (Roychowdhury et al. 2011):

1) To appropriately identify patients who could benefit from biomarker driven oncology protocols
2) To develop an adequate informed consent process that addresses the possibility of incidental germline findings
3) To implement an efficient pipeline for analysis
4) To identify which results should be disclosed to patients
5) To complete the analysis in a clinically relevant timeline while remaining cost effective

From protocol development through project initiation, GCs have made important contributions to addressing these study goals and have become an integral strength to the MI-ONCOSEQ program. Here we present several functions GCs perform as part of the multi-disciplinary MI-ONCOSEQ team, representing largely traditional GC roles adapted to a new application. Our experiences highlight that cancer GCs can utilize existing skills to enhance patient care in the personalized oncology setting.

MI-ONCOSEQ Experience and Genetic Counselor Roles

Patient Population: Unique Aspects and Informed Consent

MI-ONCOSEQ initially enrolled adult patients, adding a separate pediatric protocol (PEDS-ONCOSEQ) in 2012. Both protocols have been approved by the University of Michigan Institutional Review Board. Patients with advanced cancer considering Phase I clinical trials are eligible for participation, with the goal of selecting individuals in whom standard of care therapies have been insufficient or non-existent, reducing the potential for undue study-related harm.

Patients considering phase I oncology trials represent a unique population. While they do not meet established criteria for vulnerable populations based on demographic and health status characteristics (Seidenfeld et al. 2008), the presence of a serious illness may create vulnerability (Nickel 2006). Phase I trial participants are strongly motivated by hope of therapeutic benefit (Catt et al. 2011; Daugherty et al. 1995) raising concern regarding how they understand and weigh risks and benefits of enrollment.

Pediatric patients are a vulnerable research population subject to additional protections ("Basic HHS Policy for Protection of Human Research Subjects" 2009). The PEDS-ONCOSEQ project mandates that tumor tissue from participants must be obtained during a standard of care biopsy or resection, whereas adult participants must consent to a research specific biopsy. Pediatric participants and their parents can be viewed as having "nothing to lose" by enrolling, in that there are no additional invasive medical procedures required for participation. Thus perceived benefits may be weighed against little to no perceived risk. Discussion of research participation in pediatric populations is also complicated by inclusion of parents and children together in the consent process (Tait et al. 2003), an issue highlighted in our case vignettes.

MI-ONCOSEQ, as a CSER site, includes a study arm focused on ethics and health communication. This group, comprised of bioethicists and health communications experts with input from GCs, worked to develop and pilot the flexible default consent. In developing the informed consent document, the team considered that patients in these populations, dealing with advanced cancer or a child with a serious illness, might prefer to focus on results directly relevant to care of their disease. This led to a provisional consent model with a flexible default option for incidental findings not relevant to treatment decisions for the current cancer. Default options influence patients' decisions in favor of the clinically preferred outcome without restricting their ability to make a different choice, aiming for a balance between best clinical judgment and respect for patient preference when possible (Halpern et al. 2007). The default position is to disclose incidental, actionable germline findings (further described below). However, participants can opt out of receiving incidental germline findings without direct impact on cancer treatment in two categories: 1) results that may have significance for biological family members; 2) results with potential medical impact for the participant. As part of the recent CSER funded work, the study team will monitor utility of the existing document and make recommendations for modifications based on experience and outcomes of patient panels, deliberative interviews, and input from other study team members and referring oncologists.

Initial Study Visit

Potential MI-ONCOSEQ participants are identified and referred by the treating physician, typically an oncologist. All participants meet with a study clinician (oncologist), study coordinator and GC as part of their initial study visit. The study clinician and study coordinator discuss the process and purpose of tumor genome sequencing to identify biomarker driven therapies, and collect samples for germline DNA analysis. The GC obtains a four generation cancer focused pedigree, and explains that this information is used to help interpret study findings. The GC discusses the difference between tumor and germline sequencing, a distinction that has proven to be confusing to patients undergoing tumor testing in other studies (Richman et al. 2011; Pellegrini et al. 2012), and the reasons why germline sequencing is important to the larger study goal of identifying therapeutic targets. This leads to

discussion of the possibility of incidental germline findings, with the GC reviewing the options for receiving incidental germline findings, answering participant questions, and eliciting their preferences for information.

Review of Germline Variants, Precision Medicine Tumor Board, and Follow Up

In the context of the MI-ONCOSEQ projects, incidental germline findings are those identified as part of the study protocol, which involves routine annotation of germline variants in a list of 160 genes in recognized cancer pathways, including all cancer-related genes recently recommended for disclosure by the ACMG (Green et al. 2013), selected by the bioinformatics team with input from GCs. GCs worked with the bioinformatics team to set parameters for variant calls, including a threshold of 2 % or less minor allele frequency in the 1000 Genomes Project, chosen to allow identification of polymorphic variants with potential clinical impact (e.g. *CHEK2* c.1100delC). Pedigrees and GC interpretation and clinical comments are entered into a shared data portal available to the bioinformatics team. This information is used by the bioinformatics team to help direct attention to potential genes of interest. For example, a family history suggestive of Lynch syndrome in a patient with a large number of somatic variants in the tumor suggests possible germline mismatch repair mutation and helps bioinformaticians target their analysis.

GCs and a molecular geneticist review the assayed germline findings in the context of medical and family history, and research publicly available mutation databases and primary literature for relevant clinical information and pathogenic classification. All variants with direct impact on treatment decisions for the existing cancer are recommended for disclosure, including any germline findings relevant to cancer pathways that may provide rationale for an existing therapeutic option or clinical trial. Incidental germline variants not relevant to treatment are divided into three groups based on categories suggested by Berg et al. (Berg et al. 2013):

1) Known pathogenic variants associated with highly penetrant autosomal dominant conditions with clearly defined medical management (e.g. *BRCA1*/*BRCA2*, Lynch syndrome genes) are all recommended for disclosure. Mutations in this category could be relevant to either or both default consent options, e.g. deleterious mutation in BRCA1 with corresponding loss of heterozygosity in a tumor would have relevance for biological family members, and potential relevance for treatment (poly ADP ribose polymerase (PARP) inhibitor trials).
2) Variants associated with moderate increases in cancer risk with no clearly defined medical management established (e.g. *APC* I1307K, *CHEK2* 1100delC); disclosure decisions for these variants are made on a case by case basis given frequent changes in available literature and risk information. These variants are discussed as part of PMTB deliberation in the context of family history. Category 2 variants potentially relevant to cancer treatment are all disclosed.
3) Heterozygous variants associated with autosomal recessive conditions not requiring modification of medical management (e.g. *SLC26A4,* the gene for autosomal recessive Pendred syndrome, also important in thyroid tumorigenesis) are not routinely disclosed, unless this information is relevant to establishing a potential therapeutic target.

As analysis of germline data becomes more efficient and knowledge regarding implications of variants expands, recommendations for results reporting will undoubtedly change. Many Category 2 genes are now part of clinically available multi-gene panels, and more of these results will likely meet our threshold for disclosure as clinical information accumulates.

GCs attend the Precision Medicine Tumor Board (PMTB), where all potentially actionable tumor and germline sequencing results are discussed by the entire multi-disciplinary team. The PMTB was created specifically to manage both somatic and germline results generated from tumor sequencing, to deliberate on clinical implications of results for treatment planning or clinical trial options, and to make recommendations about disclosure of findings. The team includes representation from oncology, molecular genetics, clinical genetics, pathology, bioinformatics, bioethics, and the phase I clinical trial team. GCs present the pedigree information and highlight any red flags for possible hereditary risk as well as the outcomes of any known previous clinical genetic evaluation or testing. A summary of the pertinent pedigree information is included in the report to the referring clinician, along with any identified red flags for hereditary cancer and availability of clinical genetic counseling and testing. GCs discuss germline findings of interest and present relevant data to aid in deliberations. GCs also make recommendations about disclosure of germline findings as part of the clinical genetics team. For germline results recommended for disclosure, GCs provide written documentation briefly describing the germline finding and clinical implications for inclusion in the research results report. After germline findings are reported, GCs work with the referring oncologist to determine appropriate clinical follow up for the patient depending on the situation. Clinical genetic counseling is offered to all patients with reported germline findings. The initial disclosure of germline findings may be done by the referring oncologist or by GCs, depending on physician preference and circumstances. Outcomes including clinical genetic counseling visits, clinical confirmation of germline findings, and testing completed in family members

are being tracked. Follow up surveys to further explore patient understanding and outcomes, as well as referring physicians preferences and needs, are currently in development with the ethics and health communications project team.

Early Findings of Interest

From project initiation in 2011 through April 30, 2013, 167 patients from 164 independent families consented to participate in MI-ONCOSEQ. Five participants (3 %) declined all germline findings; 1 (0.6 %) declined germline results with relevance to biological family members. Thirty-four patients from 34 independent families have enrolled in PEDS-ONCOSEQ; 4 (11.8 %) have declined all germline findings. The remaining patients all agreed to receive germline findings.

Four generation pedigrees were collected for 162/164 adult families (165/167 adult patients) and all 34 enrolled pediatric patients. The first two enrolled adult patients did not provide family history information; one family includes four adult siblings all enrolled in the study. Fifty-seven of 162 (35.1 %) adult participants' pedigrees had one or more red flags for hereditary cancer (Table 1); 22/57 (38.6 %) had prior genetic counseling and/or genetic testing in themselves or a family member. Seven (20.6 %) of 34 pediatric participants had one or more red flags for hereditary cancer identified in the pedigree; 6/7 (85.7 %) had prior genetic counseling and/or genetic testing in themselves or a family member. Pedigrees for patients previously seen for genetic counseling in the University of Michigan Cancer Genetics Clinic (UMCGC) were reviewed and updated; full pedigrees were obtained for patients who had prior genetic counseling outside the UMCGC.

Between January 1, 2013 and April 30, 2013, germline analysis of a panel of 160 pre-selected cancer specific genes was completed in 36 adult and 10 pediatric participants. Approximately 312 single nucleotide germline variants with a frequency of 2 % or less in the 1000 Genomes Project were identified, an average of 6.8 variants per participant. Five variants (5/312; 1.6 %) in 5 independent patients (5/46; 10.9 %) met the Category 1 or 2 thresholds for recommended disclosure. Two of the five patients did not have any personal or family history of cancer associated with the identified variant.

Table 1 Red flags for hereditary cancer

- Earlier than average age at cancer diagnosis
- Rare or unusual tumor type with known association to inherited syndrome
- Multiple primary cancers
- Two or more family members with the same or related cancers in same lineage
- Ashkenazi Jewish ancestry with personal or family history of breast, ovarian, prostate, or pancreatic cancer

Adapted from National Cancer Institute http://www.cancer.gov/cancertopics/factsheet/Risk/genetic-testing

Case Vignettes—Ethical and Counseling Issues

Ethical and counseling issues encountered since initiation of MI-ONCOSEQ highlight the importance and applicability of genetic counseling skills in this setting. The following vignettes outline a few such challenges that will likely occur with increasing frequency in the clinical setting as well.

Pediatric Participants and Discordant Desires Regarding Return of Germline Findings

Two PEDS-ONCOSEQ participants of assenting age (10–17) disagreed with their parents/legal guardians about disclosure of germline findings. Participant A was adopted and had no information on biological family members. He was accompanied to the study visit by his adoptive mother and two of her relatives. When asked about preference for receiving actionable incidental germline findings, the minor participant did not wish to be notified. However, his adoptive mother requested the information. The GC asked the participant if he would allow his mother to learn the information about incidental germline findings and he agreed, but again stated that he did not want to know the information himself. No actionable germline variants were identified.

Participant B was accompanied by his parents for initial study visit. During the consent process, he expressed interest in learning about actionable incidental germline findings, while his parents were not interested. The GC established that the participant was interested primarily out of curiosity, while his parents wanted to focus on coping with his existing illness. After further discussion, the participant was comfortable with his parents' desire to opt out of germline results. The participant died 2 months after enrollment; germline analysis was not completed prior to his death.

The final decision for return of optional incidental findings in pediatric participants of assenting age (10–17 years) legally rests with the consenting parent/legal guardian. In cases where there is disagreement, GCs have the skills and training to engage families in discussion of the risks, benefits and limitations of testing and facilitate decision making that recognizes and respects all of the parties involved, including the assenting minor when appropriate. Professional guidelines discourage testing of minors for adult onset conditions (Mazoyer et al. 1996; "Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors" 1995), although the ACMG recommends

reconsidering this approach as WGS becomes more common (Green et al. 2013). The ethical arguments for and against predictive testing in minors are extensive and well documented, but they have generally failed to consider developmental differences between adolescents and younger children and are backed by little to no supporting data (Mand et al. 2012). These arguments have also focused on testing for conditions known to exist in the family, rather than disclosing mutations identified through WGS. Our case examples highlight an area for further research. The pediatric study was designed with the parent/legal guardian as the final decision maker, but these examples indicate that further research should investigate alternative options that protect the interests of parents/legal guardians and the future interests of minors.

Known Hereditary Risk in a Family who Declined Clinical Genetic Counseling/Testing

A second dilemma faced by GCs participating in the initial research visit was establishing a boundary between clinical and research roles. GCs obtain a cancer focused pedigree for research purposes to help with interpretation of germline findings. Approximately one-third of these pedigrees had at least one feature suggestive of possible inherited risk, and some participants had a clear indication for clinical genetic testing. However, the primary purpose of the initial study visit is discussion of a complex research protocol, not provision of clinical genetic risk assessment or counseling. To minimize confusion and maintain a clear boundary between research and clinical testing, GCs have opted not to broach the topic of clinical genetic testing during a study visit unless it is specifically raised by a participant. Instead, recommendations for clinical evaluation and genetic testing are communicated during presentation at the PMTB and included in the written report returned to the referring clinician. There will be missed opportunities to provide potentially beneficial information to study participants using this approach. However, we believe this approach more fully respects participant autonomy and allows the focus to remain on the complicated study related discussion and decision making as exemplified in the following case.

Participant C enrolled in MI-ONCOSEQ as an adult following diagnosis of a squamous cell carcinoma of the thymus. Five months before study enrollment, he was referred by his oncologist for clinical evaluation in the UMCGC, but declined to schedule an appointment. A full pedigree collected at initial study visit met Amsterdam I criteria for Lynch syndrome, including young onset colon cancer in the patient's mother. Maternal relatives were known to carry a germline mismatch repair (MMR) gene mutation. The participant, his mother, and his maternal aunts and uncles were aware of the diagnosis of Lynch syndrome, but had not pursued clinical testing for the known mutation and had also declined genetic counseling despite recommendations from previous clinicians. In discussion with the GC at the study visit they did not verbalize why they had not pursued clinical evaluation. Upon enrollment in MI-ONCOSEQ, the participant opted to receive incidental findings and a germline MMR gene mutation was confirmed. This result was returned to the referring oncologist as part of the research report along with a recommendation for clinical genetic counseling. The participant and his family members have had no further contact with the UMCGC.

Participant C did not follow through with clinical genetic counseling and testing despite awareness of and access to these services as well as knowledge of his risk. His decision to receive incidental germline findings was discordant from previous actions. At-risk relatives in families with known cancer syndromes often do not pursue testing for a variety of logistical and personal reasons (Sharaf et al. 2013). There may also be stages of readiness for acceptance of clinical genetics services that impact adherence to referral recommendations (O'Neill et al. 2006). Although the patient did not verbalize his reasons, he was offered clinical services multiple times and declined. We have continued to maintain clear separation of research and clinical genetic counseling for study participants, recognizing that individuals have a right to make autonomous decisions about clinical services separate from their decisions to participate in research.

Conclusion

The primary goal of the MI-ONCOSEQ project has been to implement WGS for targeted oncology therapy. Recognizing the broader implications of this testing, the project team included GCs in protocol development from conception through implementation. This allowed for GC input on crucial project elements, including management of potential incidental germline findings. As the MI-ONCOSEQ project has progressed, GCs have participated in re-evaluation and adaptation of the protocol, a process requiring intra-team communication and flexibility. GCs have applied traditional skills including communicating complex genetic information, educating and gathering feedback from the community in development and implementation of the flexible default consent, helping participants make informed decisions for incidental findings, and educating and being a resource for physician colleagues and other study team members. Participation in the PMTB has strengthened existing relationships with oncologists and increased our interactions and visibility with specialty oncologists who may not typically care for patients with hereditary cancers (e.g. thoracic, head and neck, sarcoma) creating new opportunities for education and collaboration.

Our experiences with MI-ONCOSEQ demonstrate that GCs have important existing skills that can be applied in multi-disciplinary care teams implementing precision

oncology, another non-traditional area of practice. Our involvement in a large research project provides multiple opportunities to engage with patients and physicians in the precision oncology setting. While involvement at this level may not be feasible for clinical GCs, there are aspects of our experience that could be applied outside of a research context. Broader use of WGS in oncology treatment decision making and ACMG recommendations for active interrogation of germline tissue in tumor-normal dyads suggests that GCs will have increasing opportunities for involvement in this area (Bombard et al. 2013). Coping with the data generated from WGS in both the research and clinical settings will require GCs to develop and enhance understanding of existing tools and databases available for variant classification. This will be an important topic for training programs and continuing education to address. We encourage GCs to embrace these opportunities as a natural extension of their existing skills.

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Conflict of Interest Jessica N. Everett, Shanna L. Gustafson, and Victoria M. Raymond declare that they do not have any conflicts of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the study.

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