Pediatric Cancer Genetics Research and an Evolving Preventive Ethics Approach for Return of Results after Death of the Subject

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Introduction

In the pediatric clinical setting, the parent/guardian will almost always be the authorized representative and designated recipient of clinical and research results, making the issue of to whom results should be returned in the pediatric setting less complex than in adult settings. It is also clear that, in genomic research related to pediatric diseases such as cancer, results may be of considerable clinical, ethical, and personal significance for parents in a number of ways, including a genomic explanation of the origin of their child's cancer, implications for the genetic testing and medical care of other siblings and of the parents themselves, and reproductive planning with regard to the recurrence risk for future children to have an increased risk of cancer. However, what remains unclear is which results should be dis-

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closed, and under what circumstances, to parents of deceased children.

Generally, whether and to whom results of genomic analysis should be returned after a research subject has died is problematic. According to current federal regulation of human subjects of research, when a research subject dies, he or she is no longer a human research subject. Institutional review boards (IRBs) therefore do not provide guidance regarding return of genomic results in this scenario because doing so is not under their purview. There are no clear guidelines for how to responsibly manage this problem.

The improvement of quality in the processes of patient care emphasizes the professionally responsible minimization of variation in the patient care processes.[1] In the absence of guidance for investigators and IRBs that oversee research in pediatric genomics, there is potential for great variation in approaches from institution to institution and even among investigators within a single institution. Such uncontrolled variation can create ethical conflicts, but is preventable. The purpose of this paper is to provide a preventive ethics approach in the return of genomic results to parents in the research setting.[2] It is based on our long-term experience with research protocols focused on genetic susceptibility to childhood cancer.

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Selective Literature Review

To set the stage for the proposed preventive ethics approach, we selectively review the current literature. Our goal in doing so is not to undertake a systematic review of the literature but to place the preventive ethics approach in the context of proposals to manage return of results in the clinical and research setting, and the preferences of research subjects and their parents and family members.

A. Return of Results in the Clinical Setting

In the clinical healthcare setting, it has been suggested that a plan for the return of results, including genetic test results, in the event of the patient's death be agreed upon during pre-test counseling, either by a genetic counselor or a physician.[3] In the United States, under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule, protected health information (PHI) can legally be shared with family members post-mortem, unless doing so is inconsistent with the prior expressed preferences of the deceased.[4] The American Medical Association also advocates for maintaining confidentiality of medical information post-mortem, and suggests that decisions about disclosure should balance the potential harm to individuals who may be identified by the information, potential benefit to at-risk individuals, the patient's previously stated wishes, and the impact of disclosure on the deceased's reputation.[5] Regarding genetic information, two United States state court cases have addressed the obligation of physicians to warn family members of a genetic risk of disease, with different outcomes. In New Jersey, it was decided that there is a duty to warn immediate family members of the risk of inheriting a genetic condition. However, the Florida Supreme Court determined that this duty was satisfied by warning the patient of the potential risk to family members.[6] There may also be state specific statutes that address disclosure of genetic information after death. For example, Texas state law specifies, "genetic information may be disclosed without an authorization…if the disclosure is: made to provide genetic information relating to a decedent and the disclosure is made to the blood relatives of the decedent for medical diagnosis."[7]

B. Return of Results in the Research Setting

The considerations regarding return of results following a patient's death become more complex in the research setting. In the United States, the regulations for the protection of human research subjects do not address disclosure of research results after death because once an individual is deceased, he or she is no longer considered a human subject.[8] The HIPAA Privacy Rule allows for the disclosure of PHI, including research results, to family members and to the authorized representative of the deceased, who then may grant permission to release such information to other individuals.

Studies have shown that in most cases research participants and family members feel that research results should be shared with family members after death. In an assessment of adult biobank participants' preferences, most individuals expressed a desire for their

genetic research results to be returned to their next of kin or a specified representative after their death, and expressed a desire to share the results with their primary care physician.[9] A survey of the family members of deceased adult men previously enrolled in *BRCA2* studies felt they had a right to know results that may have an impact upon their personal risk management decisions.[10] Parents of children with cancer and inherited diseases expressed a strong right to receive results of genomic research directly related to their child's condition, including the situation in which a child has died.[11]

or their physicians. The protocol was not specific to RTS; investigators also included families with other unusual patterns of childhood cancer suggestive of an underlying cancer susceptibility gene as described in Case 2.

In 1999, the first report in *Nature Genetics* identified *RECQL4* mutations in 4 of 6 of RTS families analyzed.[14] At that time, BCM investigators began to perform research sequencing of the *RECQL4* gene of all RTS families enrolled in H7207, resulting in the identification of pathogenic mutations in about 65% of the patients with RTS and including almost

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Illustrative Case Studies of the Challenges of Return of Results in Pediatric Genomic Research

A. Two Cases of Rare Disorders Studies

Rothmund-Thomson Syndrome (RTS) is a rare autosomal recessive condition characterized by a distinctive rash (poikiloderma) which first appears in infancy. Other associated features include short stature, abnormalities of the hair and nails, juvenile cataracts, and skeletal abnormalities.[12] In the late 1990s, case studies began to accumulate demonstrating the connection between RTS and osteosarcoma.[13] In 1998, investigators at Baylor College of Medicine (BCM) initiated a human subjects protocol to study the molecular basis of familial cancer susceptibility (H7207), with an initial focus on identifying the cancer risk in RTS and identifying the causative gene. Given that all research procedures were being performed in a laboratory not regulated by the Clinical Laboratory and Improvement Amendments (CLIA) law, and the goal of the project was gene discovery, the protocol, consent forms and the consent process clearly stated that there were no plans to provide results to subjects

all patients with RTS and osteosarcoma.[15] During this same time period, study families and their physicians who had learned of the discoveries routinely requested *RECQL4* test results from study investigators. Despite extensive efforts to make clear at the time of study entry that research results would not be provided, many families and their physicians were disheartened when their requests were denied.

Case 1: In 1999, the physician for an RTS patient contacted the BCM investigators about joining the H7207 study. The samples from the child and parents were included in the molecular analysis of the *RECLQ4* gene and pathogenic mutations were identified in the child's sample as part of that study. In 2003, the child died from osteosarcoma, the malignancy most frequently seen in RTS patients. Several months later, the parents and their physicians contacted the BCM investigators, as the parents were currently expecting a second child and requested the *RECQL4* research information. The requested information was specifically for prenatal counseling and testing purposes as the pregnancy was at 25% risk of being affected by RTS (given the autosomal recessive nature of the disease). The family had identified a clinical laboratory in their home country that was willing to confirm research findings provided by the investigators. The H7207 study investigators retained the only biological sample that existed from the affected child (now deceased) and, at the time, no lab was offering parental *RECQL4* testing outside of confirming research results. Given these circumstances, BCM study staff

rapidly requested and obtained permission from the BCM IRB to provide these *RECQL4* research results to the physicians and laboratory willing to conduct confirmatory clinical testing. Parental carrier status was confirmed and the parents were informed that the fetus was found to carry both pathogenic mutations as had their child with RTS.

Change in protocol: After this experience, the H7207 protocol and consent was modified to ask each subject (or parent) whether they wanted to be provided return of results and to whom the results should be returned to (the family or to a health care provider). Research results would be returned to families only if the research findings had undergone peer review for publication in a scientific journal and were found to be "clinically important." This differs from the approach used by some institutions where results must be returned to families in order to be included in a publication. Upon return, it is recommended to the parents that the research results be confirmed in a laboratory subject to CLIA prior to clinical usage.

Case 2: Over a period of several years, two siblings in early childhood were diagnosed with advanced tumors of the same organ, which is an extremely rare finding and highly suggestive of a genetic predisposition to cancer. As a part of the clinical work-up after the second sibling was diagnosed, genetic testing for all syndromes currently known to be associated with this pediatric tumor type revealed no significant findings. On the advent of whole exome/genome sequencing research initiatives, family members were entered into research studies at BCM (parents entered a BCM genome sequencing study for Mendelian disorders) and another institution caring for the child. Investigators from both institutions collaborated on a research study to try to identify the underlying cause of cancer in the family. Extensive use of genomic technologies (whole exome and genome sequencing of blood and tumor samples) was performed. Despite this effort, the etiology of the pediatric cancers in this family remains unclear. The absence of answers to the question, "why?" has been difficult for the family. They are left with concerns for risks to their remaining children and concerns of having additional affected children without a known genetic diagnosis. Over many years, the parents of these children have contacted BCM researchers at least yearly requesting updated information including information that might be relevant to other medical problems within the family, or questions about reports in the lay press about new genetic findings (both common and rare genetic changes) and their relevance to the cancer risk within the family.

Summary of experience from rare disorder research: These cases illustrate the additional complexity of research studies for rare diseases where there is frequent interaction between patients, caretakers and a small number of researchers. Unlike biobanks or genome-wide association (GWAS) studies, the information that can potentially be elicited has a higher likelihood to directly have an impact upon families. Furthermore, the principal investigators may have direct and long-term relationships with families, furthering the likelihood of opportunities to disclose results. Case 1 shows that participating subjects and their physicians may have expectations to receive results, even when agreeing to enroll in a study that explicitly states that results will not be returned. This is consistent with studies that have shown that participants have difficulties in comprehension when giving informed consent in the setting of clinical trials. This includes confusion regarding the purpose and nature of trials, study procedures, and confusion between clinical trial steps and clinical care.[16] Both cases illustrate that over time families may be faced with uncertainties, such as with family planning, and may turn to study investigators in the hope of obtaining relevant information. Moreover, if a protocol excludes return of results, then there may be scenarios in which clinically relevant information would be withheld from participants who may not have other means of obtaining that information. This was illustrated in Case 1 where the research results provided diagnostic information to the family in a successive pregnancy that would have otherwise been unavailable.

Parental interest in return of results: Consistent with published reports, parents are very interested in the return of results. Since 2003, when return of results was introduced into H7207, an additional 352 individuals (predominantly pediatric patients) have been enrolled and 345 (98%) of the adult subjects or the parents of the pediatric age subjects have requested that clinically significant results be returned. Of those who elected to receive results, 15% wanted the results returned to a health care provider of their choice, 6% asked that results be returned both to themselves and a health care provider, and 79% requested that results be returned to them directly. However, Case 2 highlights the scenario, which is true in many families, where despite the possibility of returning results, clinically relevant results may not become available. The definition of what is clinically relevant may also differ (or be unclear) between families, investigators, and institutions.

The investigators in these cases may also be the clinical providers for study patients and families. Therefore, the fine line between research and clinical care may be more frequently blurred. As genomic research studies begin to utilize clinical testing in the context

of a research protocol, the lines between clinic and research become more difficult to distinguish. The next section will address three case examples of return of genomic results of a clinically available test in the setting of a research study.

B. Baylor College of Medicine Advancing Sequencing in Childhood Cancer Care (BASIC3)

The National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) funded Baylor College of Medicine Advancing Sequencing in Childhood Cancer Care (BASIC3) study, one of the NIH Clinical Sequencing Exploratory Research program projects, examines the clinical utility of tumor and germline WES in the care of childhood cancer patients. The human subjects protocol (H30755) was initially approved in 2012 by the BCM IRB, which is also the IRB for Texas Children's Hospital (TCH), the study clinical site. Study enrollment is offered to all patients with newly-diagnosed solid tumors (including central nervous system [CNS] tumors) under the age of 18 years who undergo their initial tumor surgery and have ongoing oncologic treatment at TCH, and have at least one parent who speaks English or Spanish.[17] As a part of the study, whole exome sequencing is performed on a sample of both blood and tumor tissue in a lab subject to CLIA using similar methods to those previously described.[18] After the germline and tumor WES reports are generated (turnaround time being 3 to 4 months), they are placed into the electronic health record and disclosed to the parents by the patient's primary oncologist and study genetic counselor. Thus, this study specifically overlaps the clinical and research settings, as the clinically validated exome results performed through participation in the protocol are deposited in the medical record and available to the physicians and other medical professionals caring for the patient and the parents.

Although it was anticipated to be uncommon, if the patient died prior to disclosure of the exome results, the initial protocol detailed contacting the family through the primary oncologist. The disclosure could be done in person or by phone in accordance with the family's preferences. Following the disclosure of results, the family would be provided with a counseling letter that would also be placed in the electronic health record. In practice, failure to disclose results prior to the child's demise sometimes occurred if the family became overwhelmed with their child's cancer care or if the child was enrolled in a cancer treatment protocol at another institution. The cases outlined below discuss scenarios in which results were returned or attempted to be returned after the death of the research participant in this study.

Case 3: A 5-year-old child was enrolled in the BASIC3 study based on the diagnosis of adrenal cortical carcinoma (ACC). This tumor type has a strong correlation to a rare cancer susceptibility syndrome, Li Fraumeni syndrome, associated with changes in a gene called *TP53*.[19] Germline WES identified a novel germline *TP53* variant which was felt to be the cause of the child's ACC and diagnostic of Li Fraumeni syndrome. These results were reported by the laboratory one month after the child's death. Working with the primary oncologist, the family returned 5 months after the death of the child to an affiliated hospital to discuss the results of the genomic testing. The parents, the primary oncologist, a study PI (clinical geneticist), and a social worker were all present at the disclosure visit. Much of the initial discussion surrounded events related to the death of the child. Only after those questions were answered did the parents want to discuss the genomic test results. Recommendations were made for additional family members to be tested for the same *TP53* variant found in the proband, and the family has followed up with these recommendations.

Case 4: A 3-year-old child was enrolled in the BASIC3 study based on the diagnosis of Wilms tumor (kidney cancer). The WES results showed no actionable tumor or germline mutations. The results became available 2 months prior to the child's death, but the disclosure visit was unable to be scheduled during this time due to the child's illness. The disclosure visit was ultimately scheduled 11 months after the child's death and was held in the oncology clinic. The parents, study PI (clinical geneticist), study genetic counselor, and the primary oncologist were present. Similar to Case 3, the primary focus of the conversation centered on the care of the child in the latter portion of illness, followed by a relatively short discussion of the genomic test result.

Case 5: A 3-year-old child was enrolled in the BASIC3 study based on the diagnosis of malignant melanoma. The tumor report identified a pathogenic mutation that had also been identified through other test methods and the germline report contained no significant findings. The WES results became available 3 days prior to the child's death and were provided to the treating oncologist but were not disclosed due to the critical nature of the child's illness and lack of additional findings. The disclosure was scheduled with the parents one month following the child's death and was done over the phone by request of the family. The father, primary oncologist, study PI (also an oncologist), and study genetic counselor were present on the call. Upon reaching the father, he felt that he was not ready for the conversation. He requested that the counseling letter and results simply be sent to the family and not discussed further on the phone.

The counseling letter provided to each study family includes a detailed description of test results written in family friendly language and includes contact information for study staff. The study protocol does not require the family to complete the disclosure process to obtain this information; therefore, the counseling letter was provided to the father as requested.

Case 6: A 9-year-old child was enrolled on the BASIC3 study based on the diagnosis of osteosarcoma. The WES results contained no significant findings and became available 3 months prior to the death of the child. However, by this time the child had transferred care from the home institution to another institution for enrollment into a clinical trial and thus there were no opportunities to disclose the results during medical visits. After the death of the child, the family was reached by the study coordinator and they expressed a desire to learn the results. However, several attempts have been made to contact and/or meet with the family and the family has not returned the calls from the study team.

Modification of protocol based on experience: These cases from the BASIC3 clinical sequencing study highlight several lessons learned in the process of returning results to the families of deceased patients. The first of these relates to timing: given the family in crisis, the results of genomic testing may not be an immediate priority of the family. In the cases involving return of results, even in light of significant findings, observations showed that families were in greater need of discussing the clinical course and loss of their child rather than the results of testing. In some cases, families expressed interest in the information but were not prepared to engage in detailed discussion; some families have failed to follow-up altogether despite knowledge of availability of results in the deceased child's medical record.

Based on lessons gleaned from the experiences of return of results of deceased patients, the study protocol has been adapted to better meet the needs of families. The plan for contact of family and return of WES results coordinated through the primary oncologist (and based on parental preference) remains in place. However, adjustments were made to the study protocol in the event that the study team is unable to schedule the disclosure. Given that WES results are in the electronic medical record, a counseling letter describing WES results is placed within the medical record and the oncologist is notified. A certified letter is then sent to the family notifying them that results and a counseling letter are available and have been included in their child's medical record. The family is provided the option to contact their child's oncologist or study staff at any time to discuss these results or to request that we provide this information to another physician of their choice. Since this protocol modification was approved, certified letters are being sent out after three unsuccessful attempts to reach the family over time. However, choosing a consistent window of time, i.e., 6-12 months following the death of the child, during which letters will be mailed could be considered.

A preventive ethics approach uses the informed consent process to anticipate and seek to minimize ethical challenges that can be expected to arise in a specific clinical context. In pediatric genomic research, these potential ethical challenges are shaped by the timing, nature, and scope of results to be returned. A successful preventive ethics approach should therefore address the risks of non-disclosure, be sensitive to timing, take study design and the types of results being disclosed into account, and be responsive to ethical concerns.

Elements of the Preventive Ethics Approach

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A. Ethical Concerns

Rights specific to child research participants can be interpreted from the 1989 Convention on the Rights of the Child, including foremost consideration of the best interests of the child, the right to the highest attainable standard of health, and the right to be heard, which evolves with increased maturity.[20] Required assent, including respect for dissent, based on the patient's age, maturity, and psychological state during the informed consent process ensures protection of these rights. Parental duty within their authority for decision making must be weighed with the child's right to autonomy and an open future, as the best interests of the child "is embedded in and dependent on the interests of the family unit."[21] Avard et al. stress, "in the context of pediatric research, it is very important to be aware of the 'familial context' of the return of 'individual' results."[22] The researcher must balance ethical principles while considering both the child and the parents as a part of a "tripartite relationship" among the child, parent and researcher.[23] This is especially applicable in the context of genomic testing where results may have direct impact on the parents, their other children, and extended family members. Additional complexities such as biological relationships, returning results in the context of divorce, as well as identifying the appropriate legal guardian for return of results must also be considered as a part of this relationship. As a part of the BASIC3 protocol, one parent is identified as the "primary parent." It is only required that the primary parent be present for disclosure of results. However, given that parental samples are requested for result interpretation, it is explained to each parent at the time of enrollment that they may receive information regarding their own genetic status as part of participation within the study. It is also explained that this information may be included within the child's report. Although parental samples are encouraged, a parent can decline to provide a sample and this will not affect the child's eligibility for the study. The study team encourages both parents to be present at the time of disclosure when possible and offers the opportunity for any absent parent to discuss research results with a study genetic counselor if no legal reason, e.g., custody rulings are in place to prevent this. Finally, researchers may have an ongoing clinical relationship with the pediatric participant and his or her family members, and therefore may feel additional responsibility towards the rights of the patients and their family members.

B. Risks of Non-Disclosure

Given the lack of guidance for return of results after the death of a research subject, investigators may design and have approved protocols that do not provide for return of results. However, as described in Case 1, there are risks to families of protocols that do not allow for return of results. Many years after the death of the subject the research results may be of significant interest to the family and, given the death of the child, there may be no other option to the family for obtaining this information other than the return of research results.

Conversely, some parents may refuse the offer of return of results. The ethics of informed refusal include an obligation to explain to parents the risks they are taking, of which they may be unaware. There are risks to parents, siblings, and future children of non-disclosure when results have clinical significance for them or might come to have such significance in the future. In addition, there may be the risk of a kind of "non-buyers' remorse" in which not having results may be troubling to parents for many years. The purpose of informed refusal is not to pressure parents but to support them in reaching an informed and deliberative decision not to receive results.

C. Timing

Consistent with other reports, our experience is that almost all parents request research results when provided the opportunity to receive them when their child is entering a research protocol. However, parents may not want the results in the immediate period, or even within a year, of the child's death. At that time, their focus tends to be on the continued coming to terms with their profound loss, which could subtly distort or even undermine the disclosure process, especially helping parents cope with what can often be cognitively demanding information. Some parents may not want information until several years later, prompted by planning for or the clinical evaluation of a current pregnancy. Thus, investigators need to take this extended timeframe into account when planning for return of results.

D. Importance of Study Design and the Type of Results to Be Disclosed

There is much ethical debate about the return of genomic research results, both during a participant's life and after death.[24] There is also ongoing dialogue about the special considerations for returning results in the pediatric setting.[25] However, not enough attention has been paid to how study design influences the types of results that are generated, which affects decisions about the return of results. For example, results from a large-scale GWAS study, which studies the association of common variations in the genome with disease, may have less immediate clinical relevance to

a patient participant's family than results from a small study of a rare disease that has the potential to identify a mutation associated with a high risk of severe disease within a family. Whole exome sequencing (WES) and whole genome sequencing (WGS) examine all coding genes or the entire genome respectively for both rare and common genetic variation and therefore opens the doors to the possibility of incidental findings unrelated to the original indication for testing.[26] As research moves into the genomic era and clinical tests are being used in research settings, the potential for identification of incidental findings increases and the boundary between research and clinical care will become more difficult to define as will the scope of return of results.[27] When planning for the disclosure of research results, it is important to distinguish the types of results that will be returned and whether they will include only those related to the indication for research participation or also include incidental findings.[28] A lack of clarity as to what will be disclosed, whether it be findings of unclear significance, incidental findings unrelated to the child's illness or an absence of clinically significant findings can complicate the disclosure to a family who has recently lost a child, particularly as parents may be trying to seek answers as to the cause of their child's illness or address concerns for siblings or future pregnancies.

E. Importance of a Protocol to Improve Quality

A simple approach to the improvement of quality is to "do it the same way every time." A more sophisticated approach is to "do it the right way every time." The latter increases the likelihood of professionally responsible minimization of variation, as variation in process may result in variation in quality of disclosure. A protocol to guide the preventive ethics approach should be understood in the context of improving the quality of return of results in pediatric genomic research. It is therefore essential to anticipate possible research results and have a clear protocol for return of results after the death of pediatric research participants. When appropriate, this should be specified during informed consent and patient participant and family preferences should be considered. The informed consent process and procedures for returning genomic research results to pediatric patients and their families must be a particularly flexible process, involving the parents and adjusting to the increasing capacity of the patient's ability to assent, and eventually consent upon the age of majority.

A particularly significant issue in return of results after death in the pediatric setting is the balance between the priorities of a grieving parent and the need for flexibility on the setting, method, and timing of disclosure. As described in our case studies, even in the setting of having medically significant genomic results to return, parents often wanted to spend more time discussing the clinical care and treatment of their child, and particularly events around the time of death, with caregivers (who may also be involved in the research study). Some families either actively or passively declined the discussion of genomic test results in this scenario. Over time, this information may grow in importance to families, particularly when planning future pregnancies or care for siblings of the deceased proband. For this reason, it will become increasingly critical to build a mechanism into return of results protocols that makes participating families aware that research results are available to them and that these results can be disclosed at the time most appropriate to the circumstances of the family even if the initial research goals of the study have been completed.

Conclusion

The return of research results after death specific to the pediatric cancer genetic setting has unique complexities. Within any pediatric setting, researchers are working with a family unit that extends beyond the proband. Genomic research results may affect not only the child but parents, siblings, and future reproductive decision making. For many families, the possibility of return of results is promising in their search for answers. However, in the context of the loss of a child, a family may have more immediate needs, such as having questions answered about the end-of-life care for their child and coping through the grieving process itself. For this reason, it is important to create a preventive ethics approach to the return of results after death that make results available to families in a protocol that supports flexibility for this to be done based on the family's needs and preferences when possible. The experiences of BCM researchers highlighted here demonstrate that this may need to be a fluid process, but overall, the ability to provide families with the option for return of results is welcomed by the majority of families. Including a well outlined protocol for return of results after death into IRB protocols will become even more important given the increasing development of genomic studies that balance the fine line between research and clinical care.

Acknowledgement

The work described in this application was supported by the National Human Genome Research Institute (NHGRI)/National Cancer Institute (NCI) #1U01HG006485 grant to Drs. Plon and Parsons. This work was also supported in part by the National Institutes of Health (NIH), NHGRI #R21HG006594-01 and NIH,

NCI and NHGRI #1-R01-CA154517 (Petersen, Koenig, Wolf, PIs). All views expressed are those of the author and do not necessarily reflect the views of NIH, NCI, or NHGRI.

References

1. L. B. McCullough, "An Ethical Framework for the Responsible Leadership of Accountable Care Organizations," *American Journal of Medical Quality* 27, no. 3 (2012): 189-194.
2. F. A. Chervenak et al., "Clinical Guides to Preventing Ethical Conflict between Pregnant Women and Their Physicians," *American Journal of Obstetrics and Gynecology* 162, no. 2 (1990): 303-307.
3. B. D. Riley et al., "Essential Elements of Genetic Cancer Risk Assessment, Counseling, and Testing: Updated Recommendations of the National Society of Genetic Counselors," *Journal of Genetic Counseling* 21, no. 2 (2012): 151-161.
4. U.S. Department of Health & Human Services, "Health Information of Deceased Individuals," *available at* <http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/decedents.html> (last visited August 19, 2015).
5. American Medical Association, Opinion 5.051 - Confidentiality of Medical Information Postmortem, *available at* <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion5051.page?> (last visited August 19, 2015).
6. *Pate v. Threlkel*, 661 So.2d 278 (Fla. 1995); *Safer v. Pack*, 677 A.2d 1188 (NJ 1996).
7. Texas Constitution and Statutes, TX. Labor Code. Sec. 21.4031 Exceptions to Confidentiality, *available at* <http://www.statutes.legis.state.tx.us/Docs/LA/htm/LA.21.htm#21.401> (last visited August 19, 2015).
8. 45 C.F.R. § 46.102 (2014).
9. N. L. Allen et al., "Biobank Participants' Preferences for Disclosure of Genetic Research Results: Perspectives from the OurGenes, OurHealth, OurCommunity Project," *Mayo Clinic Proceedings* 89, no. 6 (2014): 738-746.
10. E. Ormondroyd et al., "Disclosure of Genetics Research Results after the Death of the Patient Participant: A Qualitative Study of the Impact on Relatives," *Journal of Genetic Counseling* 16, no. 4 (2007): 527-538.
11. C. V. Fernandez et al., "Attitudes of Parents toward the Return of Targeted and Incidental Genomic Research Findings in Children," *Genetics in Medicine* 16, no. 8 (2014): 633-640.
12. L. L. Wang et al., "Clinical Manifestations in a Cohort of 41 Rothmund-Thomson Syndrome Patients," *American Journal of Medical Genetics* 102, no. 1 (2001): 11-17.
13. I. Cumin et al., "Rothmund-Thomson Syndrome and Osteosarcoma," *Medical and Pediatric Oncology* 26, no. 6 (1996): 414-416; A. Leonard., "Osteogenic Sarcoma in the Rothmund-Thomson Syndrome," *Medical and Pediatric Oncology* 26, no. 4 (1996): 249-253; J. S. Green et al., "Rothmund-Thomson Syndrome Complicated by Osteosarcoma," *Pediatric Radiology* 28, no. 1 (1998): 48-50.
14. S. Kitao et al., "Rothmund-Thomson Syndrome Responsible Gene, RECQL4: Genomic Structure and products," *Genomics* 61, no. 3 (1999): 268-276.
15. L. L. Wang et al., "Association between Osteosarcoma and Deleterious Mutations in the RECQL4 Gene in Rothmund-Thomson Syndrome," *Journal of the National Cancer Institute* 95, no. 9 (2003): 669-674.
16. V. Sanchini et al., "Informed Consent as an Ethical Requirement in Clinical Trials: An Old, But Still Unresolved Issue. An Observational Study to Evaluate Patient's Informed Consent Comprehension," *Journal of Medical Ethics* 40, no. 4 (2014): 269-275.
17. S. Scollon et al., "Obtaining Informed Consent for Clinical Tumor and Germline Exome Sequencing of Newly Diagnosed Childhood Cancer Patients," *Genome Medicine* 6, no. 9 (2014): 69.
18. Y. Yang et al., "Clinical Whole-Exome Sequencing for the Diagnosis of Mendelian Disorders," *New England Journal of Medicine* 369, no. 16 (2013): 1502-1511.
19. J. D. Wasserman et al., "Prevalence and Functional Consequence of TP53 Mutations in Pediatric Adrenocortical Carcinoma: A Children's Oncology Group Study," *Journal of Clinical Oncology* 33, no. 6 (2015): 602-609.
20. M. H. Zawati et al., "The Best Interests of the Child and the Return of Results in Genetic Research: International Comparative Perspectives," *BMC Medical Ethics* 15 (2014): 72.
21. *Id.* citing L. F. Ross et al., "Technical Report: Ethical and Policy Issues in Genetic Testing and Screening of Children," *Genetics in Medicine* 15, no. 3 (2013): 234-245.
22. D. Avard et al., "Pediatric Research and the Return of Individual Research Results," *Journal of Law, Medicine & Ethics* 39, no. 4 (2011): 593-604, at 601.
23. *Id.*
24. B. Chan et al., "Genomic Inheritances: Disclosing Individual Research Results from Whole-Exome Sequencing to Deceased Participants' Relatives," *American Journal of Bioethics* 12, no. 10 (2012): 1-8; G. P. Jarvik et al., "Return of Genomic Results to Research Participants: The Floor, the Ceiling, and the Choices in Between," *American Journal of Human Genetics* 94, no. 6 (2014): 818-826.
25. Zawati et al., *supra* note 20; E. W. Clayton et al., "Addressing the Ethical Challenges in Genetic Testing and Sequencing of Children," *American Journal of Bioethics* 14, no. 3 (2014): 3-9.
26. A. L. McGuire et al., "Returning Genetic Research Results: Study Type Matters," *Personalized Medicine* 10, no. 1 (2013): 27-34.
27. S. M. Wolf, "Return of Individual Research Results and Incidental Findings: Facing the Challenges of Translational Science," *Annual Review of Genomics and Human Genetics* 14 (2013): 557-577.
28. Avard et al., *supra* note 22.