Reporting Unwelcome Unanticipated Findings of Diagnostic Genomic Studies

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Keywords: genomics, genetics, unanticipated findings, autonomy

The introduction of comparative genomic hybridization has revolutionized clinical genetics. It is used as a routine approach to the workup of developmental delays and multiple malformations.[1-3] By subdividing chromosomes into their submicroscopic components, clinicians can detect minute losses or duplications of stretches of genetic material. The evolving technology has brought a new level of detail with single nucleotide polymorphism (SNP) array.

SNP arrays enhance diagnostic success due to its ability to uncover small regions of Loss of Heterozygosity (LOH), which are significant in the diagnosis of autosomal recessive diseases. However, SNP arrays also have the ability to expose large and/or numerous regions of LOH. These larger regions of LOH are presumed to have been inherited from two parents who share alleles derived from a recent common ancestor (consanguinity).

The American College of Medical Genetics and Genomics (ACMG) recognizes that there is insufficient research to make evidence based recommendations regarding the disclosure of results unrelated to the primary goal of the genetic testing.[4] Recently, the ACMG presented a list of genetic diseases that should be disclosed to the patient when encountered as an incidental finding[4], but the ACMG has yet to present recommendations for disclosing previously unknown consanguinity. To explore the ethical considerations surrounding consanguinity uncovered by SNP array we offer a hypothetical case and provide a formal ethical analysis.

Case Report

Courtney is a healthy 36-year-old woman who comes to a clinic with her husband Larry for evaluation of a new pregnancy. The ultrasound reveals a fetus, appropriately sized for 18 weeks gestation with multiple anomalies

including encephalocele, omphalocele, and polydactyly. The differential diagnosis includes a chromosomal abnormality and Meckel-Gruber syndrome, a rare autosomal recessive disease. Indicated by maternal age and ultrasound findings, an amniocentesis is performed. Karyotype analysis reveals a normal chromosomal configuration at the microscopic level of analysis, but SNP array is pursued. Results show a high degree of LOH (11%) consistent with a parental half-sibling relationship. One of the regions displaying a high degree of LOH is a portion of the long arm of chromosome 17, the region which includes the gene associated with Meckel-Gruber syndrome type 1.

Courtney, an only child, was born in Seattle, Washington. Courtney's parents attended medical school in Chicago. During that time her parents experienced fertility problems and consulted a specialist to achieve conception. Larry is also an only child born in Chicago to two faculty members at a public high school. Larry earned his bachelor's degree in Miami, FL, and Courtney obtained hers at UCLA; they met while studying law at Boston College.

Upon further questioning it is discovered that Larry's parents also experienced infertility. Unknown to both Larry and Courtney, their mothers received semen from the same donor: a graduate student working on his PhD in Genetics at Northwestern.

Analysis

Principlism has been enshrined in the medical ethics literature for the past thirty years as the preferred basis for ethical analysis, in part, because it purports to allow for critical ethical analysis that is not founded on any religious tradition. It enjoins us to honor patient autonomy, seek justice, and act with beneficence and non-maleficence.[5] These four principles should be honored to their full extents, with the relative value of each dependent on the context of the ethical dilemma in question. Ideally, there should be a balance between the four principles with no one principle ranking higher than the others.

That being said, western medicine places a priority on patient autonomy over the other principles.[6] Autonomy has played a major role in shaping the practice of clinical genetics, laws surrounding genetic privacy, and genetic counseling. This principle focuses attention on the importance of allowing patients to make their own decisions regarding their medical care. In order to make autonomous decisions about their reproductive future, parents have the right to comprehensive knowledge and understanding of the health risks facing their future offspring.

It is estimated that each human is heterozygous for several genes that would be lethal in the homozygous state.[7] Since there is a risk that consanguineous parents share several deleterious alleles in the heterozygous state, any future child could be at a 25% risk for more than one disorder. Given this increased risk, consanguineous unions have a lower level of genetic fitness in relation to the general population. This is manifested by increased rates of recessively inherited diseases, congenital malformations, intellectual disability, and childhood morbidity and mortality.[8]

In order to identify the most appropriate options regarding their reproductive future, parents must have full access to information about their offspring's potential conditions.[9] Failure to inform the couple of the negative biological effects of consanguinity on health will render the couple's future reproductive decisions non-autonomous, for they will be ill-informed. Now that Courtney and Larry's fetus is known to have LOH in the region that includes a gene which could explain the malformations discovered by ultrasound, they can have mutation analysis to document this. They can also be advised of 25% recurrence risk in any future pregnancy. The question, however, is whether they should be informed that they are closely related to each other and have a significant chance of other shared recessive alleles.

When considering this case it is important to determine whether exposing incidental information to Courtney and Larry is justifiable. There have been three lawsuits against physicians in the United States regarding failure to warn family members about hereditary disease risks.[10-12] The most recent of the three cases is *Molloy v Meier*. In 2003, Kimberly Molloy filed a lawsuit with the Minnesota Supreme Court against physicians who failed to diagnose her daughter with fragile X syndrome, an X-linked cause of intellectual disability. The plaintiff claimed that the physicians who cared for her child were negligent because they failed to inform Kimberly Molloy of the risk of intellectual disability in future offspring. The court held that the "physician's duty regarding genetic testing and diagnosis extends beyond the patient to the biological parents who foreseeably may be harmed by a breach of that duty."[12] In the case of Courtney and Larry, it would be unjust to reveal only diagnostic information regarding the diagnosis of Meckel-Gruber syndrome in the fetus without also discussing the broader reproductive health risks implied by the high LOH reflecting close consanguinity. This finding must be considered "actionable" because the patient can use it to guide health decisions. "Actionable" is defined as some action that may be taken by a physician to prevent a genetic-related disease or disorder from occurring, or to alter its natural progression in some way. Providing Courtney and Larry with all known necessary information on reproductive health will allow them to pursue other reproductive options with less risks.

The principles of non-maleficence and beneficence will be discussed jointly because they are best understood as the minimization of burdens and the maximization of benefits. The outcomes from uncovering consanguinity can be either beneficial or harmful depending largely on the circumstances of the scenario. Uncovering unknown genetic information has the potential to negatively impact self-esteem and self-perception.[13] In a study that reviewed families with Tay-Sachs disease, 25% of carriers and 6% of carriers' spouses felt that knowing their own or their spouse's carrier status would have affected their marriage decisions.[14] People who become aware of their genetic hereditary diseases have an increased risk of mental health issues, and are more likely to experience a significant decline in satisfaction with their relationships.[15]

We suspect that knowing of consanguineous relationships after the fact would cause many people to forego further pregnancies. Discovering unintentional consanguinity in the already highly-charged circumstances of a pregnancy or child in distress has the potential to create an even greater psychological challenge to those involved. Psychosocial stressors such as denial, worries of divorce, and other major lifestyle changes can also produce detrimental repercussions to the family dynamic.

Some physicians may feel more comfortable in choosing not to disclose consanguinity for it will avoid the negative repercussions from exposing such information. However by doing so, important information regarding the health of future children would be withheld and entailing deception. We do not believe that the clinician is at liberty to provide such selective and incomplete disclosure. Informing a couple of their relatedness provides an opportunity to pursue other safer options for expanding their family. Any short-term gain of tranquility associated with nondisclosure of reproductive risks would not honor the duty to act beneficently.

Conclusions

Clinicians who provide SNP array testing should discuss with precision the potential implications of LOH so that those signing the consent form have no ambiguity. The case of Courtney and Larry illustrates one of several plausible scenarios that can result from discovery of pronounced LOH. Other possible cases include adoption, incest, infidelity, and intentional concealment due to social stigma or legal implications. Physicians need to be prepared to discuss the risk of uncovering high LOH even though the probability of consanguinity is low. The consent form should include an explanation that disclosure will include all elements of the test results that are thought to have clinical significance, including consanguinity. The advantages and disadvantages of genetic testing vary significantly from one patient to the next. It is essential to disclose both the positive and negative repercussions of SNP array testing so that involved parties can make fully informed decisions. We find no merit in the clinician assuming responsibility for deciding what information should or should not be disclosed on the basis of it being uncomfortable to discuss.

Full disclosure is necessary to enhance patient autonomy by providing the patient with information to make an informed decision to "accept these conditions, find another physician or forego testing."[16] In the clinical encounter, embarrassment, surprise, anger, and fear are all undesirable but normal reactions which physicians and counselors must be prepared to address. More explicit and detailed communication will ensure that these emotions will be limited in any clinical encounter. We do not propose that all incidental findings should be disclosed to patients, however we believe that consanguinity is actionable in reducing reproductive risks and should be disclosed for that reason.

Genetic counselors must be prepared to provide supportive counseling for patients with incidental findings on SNP array testing, just as they do for other currently available testing methods. There may be patients who need counseling beyond what is offered in the genetics counseling office, which will require a referral to professionals skilled in psychological counseling.

As developments in genetic testing become more advanced, it is necessary to keep these ethical considerations regarding the reporting of incidental findings in mind. Practitioners must bear in mind the potential findings of genetic tests such as SNP array, and be prepared to discuss such findings, despite the potential discomfort and stressors imposed on the parties involved.

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