

Virtual Mentor

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Letting Patient Values Guide Shared Decision Making

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A bright healthy woman sought the opinion of one more geneticist as she neared the end of her reproductive life. Dedicated to disallowing her major birth anomaly from defining her, she was grappling with the ethical, moral, personal, financial, and career impact that having a similarly affected child would have on her and her husband. Copious testing including DNA microarray and consultations over the years had failed to define a syndrome, etiology, or potential recurrence risk. Maybe it was teratogenic. Maybe it was an unidentified autosomal dominant mutation with a 50 percent recurrence risk to her potential children, or maybe it was not genetic.

After decades of supporting individualized decision making in prenatal diagnosis and pre-conception pregnancy planning, this was the first case in which I felt that whole-exome testing might be clinically indicated. (Whole-exome testing looks at all parts of the patient's genome that are known to contribute to physical and health-related traits.) Although clarification of this woman's diagnosis would be unlikely to suggest treatment or cure, at least we might narrow the zero-to-50 percent estimate of recurrence risk while she was still fertile. Having identified a reliable commercial lab, I invited the patient and her husband back to consider her values about further diagnostic testing.

The visit began as usual: "There is no *right* answer to this problem of whether or not to do this genetic test; there is only the answer *you* choose as most consistent with your own values. I will help with the decision analysis. We will care for you, whatever you decide." The patient's husband stated his unconditional love and support for his bride; he considered her very beautiful and would welcome and care for a child with his wife's birth anomaly. Having lived with her functional deficits longer than she had known her husband, the patient was not so clear about how the shame-blame-guilt feelings might play out if her baby were born similarly affected.

Whole-exome sequencing (WES) would have the possible benefit of "ending the diagnostic journey." Stigmatization and life insurance discrimination already existed for this patient and would not deter testing. The prevention of recurrence could justify an appeal to her health insurer to cover the test, since finding a causative DNA mutation could be utilized for prenatal diagnosis by first trimester chorionic villus sampling (CVS), second trimester amniocentesis, or by preimplantation genetic diagnosis (PGD) after in vitro fertilization (IVF). However, the patient was adamant about not terminating an established pregnancy with or without the deleterious mutation and not "throwing out" affected embryos after IVF with PGD.

She had already rejected other options of adoption, donor egg implantation, and bypassing prenatal diagnosis of a known mutation altogether. She would be sad if her child were mercilessly teased in school as she had been, but she felt uniquely prepared to help a child with those issues.

If we found a putatively responsible DNA mutation by WES, we would need to study the patient's unaffected parents to see if one or both also carried the mutation; presence in one unaffected parent would disqualify genetic inheritance as the cause. They lived in rural Portugal—who would pay for their testing? What if the parents felt guilty, believing that they might have caused a mutation by their own behaviors or fetal exposures? Facing a diagnostic answer with an associated increased recurrence risk, would the patient decide against having biological children? If we did not find a likely mutation, some months would be wasted waiting for results. Having waited, the patient might hope for the diagnostic promise of the next great test “sometime next year.”

“What else would we learn from this test?” asked the husband. “Might we find out if my wife carries other mutations, like some of the mutations you explained from the preconception screen?” Aha! The essential question! Yes, of course, everything found on a medical test belongs to the patient. It is his or her medical record. It is his or her test result. Not knowing what we were looking for, we would be casting a large, nonspecific net and be likely to uncover collateral information. As the ordering physician, it would be my obligation to share those results with the patient, taking the time to describe what may and may not be significant, based on current knowledge, anticipating that knowledge to change and require reinterpretation over time. We may well have a DNA finding of unknown significance, except as the preliminary results of research. Variants of unknown clinical significance abound on DNA microarray testing. How would we know what was significant if we didn't look? On the other hand, how would we explain massively unknowable results to the patient or her children?

Faced with receiving uninterpretable test results, and given the value they placed on having their own child together, regardless of birth anomalies, the couple decided to decline WES at the time. After more than 3 hours of consultation and much discussion at home, they hoped that there was no risk of the patient's congenital anomaly recurring and confined themselves to choosing among the bewildering genetic screening and testing options related to their advanced parental ages.

Was enough time spent clarifying the issues? What if the discussions had occurred through an interpreter? How can a dysmorphologist or clinical geneticist or genetic counselor spend adequate time helping a single patient understand such complexities? What if the discussion needs to start by defining DNA? How can sensitive, individualized decision making about genetic testing be made available nationally? The very nature of medical ethics includes more questions than answers, but with for-profit companies advertising to the public, time for appropriate, skilled, objective but caring, decision support becomes the significant commodity.

McGuire et al. [1] recommend that the ordering physician limit study of the exome or genome to a specific set of genes to reduce confusion and false findings. When it is possible to know where to look, we do order a “DNA panel,” or sequence the suspected DNA. Unfortunately, as in the case of the patient above, we oftentimes have no indication of where those genes might be, or what else we might find. Explaining this is an essential element of truly informed consent to testing, but many people want as much information as they can get, without consideration of the myriad *true positives* they may also receive.

No field in American medicine has exploded with new information in so short a time as clinical genetics. In the dyad of the patient and doctor, it has been challenging to explain that a one-in-four recurrence risk equals a three-out-of-four chance that the problem will *not* occur. Concern for the language skills, education, culture, gender, expectations, values, and abilities of the patient is still critical. Implications of test results for the patient, the current family, and future children are daunting. It is vastly rewarding to “get it right,” helping a person choose the best path, utilizing whole-genome and -exome sequencing, under conditions of increasing uncertainty. Perhaps the next generation will learn if the answers are right.

References

1. McGuire AL, McCullough LB, Evans JP. The indispensable role of professional judgment in genomic medicine. *JAMA*. 2013;309(14):1465-1466.

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