COMMENTARY

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The Lifespan of Genetic Testing

Genetic testing is now more commonplace in clinical medicine owing largely to improvements in sequencing technology. Genetic results enable greater diagnostic certainty with important prognostic and therapeutic implications. Nevertheless, it is important to consider the longitudinal relationship created between the provider, the patient, and his or her family. This relationship can extend long beyond the initial encounter and sometimes beyond the patient's lifespan as our understanding of DNA sequence variation evolves over time. While an individual's inherited genetic defects are static, the interpretation of clinical significance is dynamic. Refined knowledge of human genetic variation represents scientific progress, but the clinical impact of revised interpretation can have the contrary effect on patient care by eroding confidence in genetic diagnoses. How do we manage this uncertainty while maintaining the trust of our patients and capitalizing on the benefits afforded by incorporating genetic diagnostics into clinical practice? We explore some of these challenges in the case of Tom (name changed).

Tom, a middle-aged man from Vermont, was diagnosed with hypertrophic cardiomyopathy. He developed worsening shortness of breath, and echocardiography demonstrated severe septal thickening. He remained skeptical of his diagnosis and presented to our institution for a second opinion. After providing pretest counseling, we arranged genetic testing, both to confirm the clinical diagnosis and to assist in screening his siblings and children. When we called to share the test results approximately 6 weeks later, his widow answered the phone. Tom had died in a motor vehicle accident shortly after our appointment. His wife, the next of kin, was notified that he had a variant in a sarcomere gene, the likely cause of his hypertrophic cardiomyopathy. She was advised that these genetic results could be used to identify whether Tom's children and siblings were at risk for developing hypertrophic cardiomyopathy and in need of regular clinical evaluations. Two years later, a notification was sent to the ordering provider by the genetic diagnostic laboratory stating that the variant was no longer considered pathogenic or disease-causing. In this setting, we felt obligated to contact Tom's widow to recommend clinical hypertrophic cardiomyopathy screening of all his at-risk family members regardless of prior genetic test results. These changing results sent mixed messages to Tom's wife. Furthermore, we wondered when our relationship with Tom truly ends.

Tom's results changed as a consequence of variant reclassification. For most disorders, each time a patient undergoes genetic testing, the entire coding region of multiple genes are sequenced to identify a DNA variant capable of causing disease. The choice of which genes to sequence is determined by the patient's phenotype. As most disease-causing variants are unique to an individual patient and their family, this process is not simply the identification of variants previously identified to cause disease, but the classification of novel previously unidentified variants. The process of variant classification is multi-faceted and increasingly guided by consensus recommendation.[1] DNA variants are deemed pathogenic based on multiple sources of information, including functional analysis, family segregation studies, population data utilizing large ethnically diverse cohorts, and computational predictive tools. Variants are generally categorized into 1 of 5 categories: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.[1] Therefore, these results should not be interpreted as dichotomous or binary, but rather as a spectrum of certainty that can evolve over time as more knowledge invariably becomes available. Generally, only pathogenic variants should be used to assist in familial evaluations to determine which relatives are at risk for disease and in need of clinical screening. It remains unresolved when and how often these classifications should be revisited. Our institution's Center for Personalized Genetic Medicine tracked and reported the rate of variant reclassification specifically in hypertrophic cardiomyopathy. From 2004 to July 2011, 4,923 individuals underwent genetic testing for hypertrophic cardiomyopathy, in whom 1,472 different DNA variants were identified. Over that time period, 214 of these variants were later reclassified as either more or less likely to cause

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disease.[2] Thus, 214 reclassifications needed to be disclosed to patients so that prior perceptions of disease risk could be recalibrated, with implications for clinical testing and follow-up. If this occurrence is not anticipated and reviewed with patients prior to testing and at the time of results disclosure, it has the potential to gradually diminish our patients' confidence in genetic testing in clinical medicine. The challenges associated with genetic test classification, reclassification, and communication with patients are relevant beyond hypertrophic cardiomyopathy. Indeed, they are common in multiple subspecialties where DNA testing is frequently used. The scope of this challenge is anticipated to grow in scale with greater incorporation of genomics in medicine.

Tom's story and experience are not unique. As our knowledge of more genetic variants grows, more questions will arise about how to disclose changing results. We must develop strategies to deal with these challenges while maintaining trust. Better approaches to enable patients to get updated variant interpretations are critical. Given the high cost of variant interpretation, laboratories often reinterpret only when a variant is seen in another case and they have limited resources to issue amended reports given lack of reimbursement for reinterpretation. Furthermore, patients are often not followed continuously by the specialists who order genetic testing, creating difficulties in determining how to get updated information back to patients. To help address this issue, genetic counseling is paramount. Generally, this is accomplished by licensed genetic counselors who are trained to communicate with patients about genetics and are prepared to navigate the complex terrain impacted by evolving knowledge, different levels of health literacy, and complex family dynamics. Genetic counselors can stress the importance of variant reinterpretation over time. This can include the suggestion that patients recontact the clinic periodically for updates or that patients follow their own variants in ClinVar and return to the clinic if new classifications are identified. ClinVar (www.ncbi.nlm.nih.gov/clinvar/) is a freely accessible archive of variants hosted by the National Center for Biotechnology Information to which many clinical and research laboratories share their variant interpretations. However, not all laboratories currently submit to ClinVar, so improved data-sharing regulations are necessary to further support this practice. And of course, not all patients will be savvy enough to use ClinVar, such that providers must develop care plans with their patients to ensure variant evidence is revisited periodically.

The genomics research community grapples with elements of this problem when it advises researchers regarding contact of research participants for the return of genetic results. Most consensus statements have recommended that clinically actionable results be returned to research participants, provided that they have not "opted out" of receiving unanticipated genetic data.[3] However, they have also advised that this obligation is not indefinite.[4] Variant reclassification and subsequent communication to patients regarding revised results is a similar problem; however, in the clinical setting it is difficult to consider this obligation as expiring after a set period of time.

As physicians and scientists, we accept that variant reclassification, essentially an advance in knowledge, can invalidate some assumptions made about disease but represents progress. However, for patients, these developments are inherently personal and can upend assumptions made about one's health and the health of their loved ones. Therefore, we justify sharing this information even when it may weaken trust among our patients. Moving forward, when ordering genetic testing, we should remind ourselves of the unspoken contract we have with our patients and the responsibilities to disclose evolving results.

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