Genomic Test Validation for Incidental Findings

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In March of 2013, the American College of Medical Genetics and Genomics (ACMG) issued recommendations for the reporting of incidental findings produced by clinical exome and genome sequencing (1, 2). This guideline on incidental findings has been controversial, because the recommendations are a departure from previous ethical concepts of patient autonomy and the reporting of adult-onset disease in children (3–5). One aspect of the incidental-findings guideline that has not been discussed is the lack of required analytical validation for the reporting of a subset of pathogenic variants known to cause severe disease. Analytical validation of any clinical test is critical before its implementation. In the case of genetic testing, clinical laboratories should neither interpret nor report sequence changes that have not been previously validated. More importantly, test results that do not meet the minimum requirements of analytical performance should not be used for clinical decision-making. The ethical concerns raised by the general clinical community in response to the incidental-findings guideline are justified. The clinical laboratory community must specifically consider the ethical and regulatory implications of returning life-changing results from tests that have not been analytically validated or have not met the minimal quality standards established by the laboratory.

The incidental-findings guideline was based on a working group appointed by the ACMG. The guideline is for clinical exome/genome laboratories to report a limited number of pathogenic DNA variants; there are 57 genes in the current guideline. The criteria on which the selection of genes was based include only “unequivocally pathogenic mutations in genes where pathogenic variants lead to disease with very high probability and where evidence strongly supports the benefits of early intervention” (2). The 57 genes are associated or causative of cancer, cardiovascular disease, or adverse drug reactions. Importantly, the guideline defines incidental findings as the “deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered” (1). Under the ACMG guideline, patients and their families do not have the ability to decline the return of results on the 57 genes. Furthermore, there is no allowance for a tiered consent. Instead, a patient may consent only to have either the test performed with the incidental findings reported or no test performed at all. For example, a pediatric patient being examined for a genetic cause of a seizure disorder cannot have an exome result restricted to genes associated with the seizure disorder. Instead, by consenting to testing the pediatric patient and their family must also agree to the return of results including those for adult-onset cancers unrelated to seizure disorders. The rationale is that the return of the pathogenic incidental finding is clinically actionable, either for the pediatric patient or for the patient’s parents. The ethical dilemmas with this type of return of results are part of an ongoing discussion (3–5).

From the perspective of clinical laboratories, the ACMG guideline raises several issues regarding clinical test validation and quality. The guideline describes the possibility that a laboratory may be split into 2 entities. One entity could “generate the raw sequencing data,” and a second separate entity could “further evaluate and interpret the sequence.” The guideline focuses on the second separate entity—evaluating and interpreting the sequence data. Laboratories (as defined by the guideline) are instructed to “seek and report mutations” from both constitutional and “normal” samples submitted with a matched tumor sample. The ACMG guideline indicates that the reported incidental findings do not have to meet the laboratory’s established quality standard for reporting (e.g., depth of sequence coverage). Furthermore, because the clinical exome/genome test may not be designed or validated for the 57 genes, results for the incidental-findings genes should come with a caveat in the report that distinguishes the (lower) quality of the incidental findings from the primary indication. There is no recommendation for confirming a positive pathogenic incidental finding by a secondary method, such as Sanger sequencing. Furthermore, the ACMG guideline does “not recommend that laboratories modify these [exome/genome] tests if they are otherwise suitable to achieve their clinical ob-
objectives” (1). Thus, this guideline recommends the reporting, but not the analytical validation, of 57 genes with clinically relevant and actionable findings.

There is indeed importance in reporting incidental findings that could lead to clinical intervention; however, the criticism of the ACMG guideline has been based on the balance of clinical action with patient autonomy. What should not be lost in this ongoing discussion is that all tests used for clinical action should be analytically sound and validated. This is a fundamental clinical laboratory concept and is mandated by regulatory statutes (e.g., CLIA). Because pathogenic results found among these 57 genes could lead to clinical intervention, their analysis must be of the highest analytical quality and must be validated according to accepted standards. It is not acceptable that a pediatric patient being evaluated for a seizure disorder be told that they have a pathogenic mutation with lifelong consequences when the result does not meet the minimum quality standards established by that laboratory or mandated by regulatory agencies. A disclaimer in a laboratory report, the guideline has suggested, does not absolve the need for test validation and minimum quality standards.

Furthermore, the ACMG guideline’s endorsement of splitting the clinical laboratory into 2 entities (raw data and interpretation) is a risky proposition for highly complex emerging technologies. Next-generation sequencing requires oversight of the entire test process. Diffusion of responsibility will occur when the raw sequencing is separate from the interpretation. Indeed, in the ACMG 2-entity laboratory model, it is unclear who is responsible for deciding that the quality of the “raw data” is sufficient for interpretation. How can a laboratory director who oversees only the “interpretation” entity track changes in quality or general interassay variation in the separate “raw data” entity? Professionals who interpret exome/genome sequencing should be intimately familiar not only with the interpretation of genetic information but also with the raw-data generation and ongoing QC measures established in the “raw” sequencing facility.

Full exome/genome sequencing is now an established clinical tool, but it is not a mature technology and still has many issues regarding the assurance of high-quality analytical data and interpretation. As an emerging technology, there should be more (not less) scrutiny of test performance and interpretation. Fragmentation of the workflow also fragments responsibility and oversight. Rather than splitting laboratories into data-producing and interpretative entities, better genetic diagnoses may be made by moving toward closer collaboration. Indeed, in genomic medicine there may be value in consolidating or formalizing the relationships between clinicians and the clinical laboratories performing the tests. Perhaps the clinicians overseeing the treatment of a patient with a complex diagnostic situation should be part of the same laboratory team that performs and interprets the exome/genome test. Thus, the clinical context of each patient tested in the laboratory would be directly linked to the clinicians responsible for managing and treating the patients.

The ethical arguments for and against the reporting of incidental findings as described in the ACMG guideline will continue for many years; however, what should not be the subject of discussion is the use of incomplete or substandard analytical information. The stakes are high for incidental findings of pathology and should be at the same or a higher analytical standard, compared with the intended primary-test indication.

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