The case for implementing sustainable routine, population-level genomic reanalysis

The recent statement released by the American College of Medical Genetics and Genomics (ACMG) highlighted the significant clinical need for periodic reevaluation and reanalysis of already reported clinical sequencing data (hereafter, genomic reanalysis).[1]

Genomic reanalysis occurs in health care when laboratories reevaluate a patient's genetic information based on new evidence of gene–disease or variant–disease associations to detect medically significant classification changes of previously reported variants or to identify new causative variants or secondary findings. Genomic reanalysis holds rapidly growing importance for both society and medicine, as stakeholders are at risk of facing potentially irreversible consequences if clinical decisions are based on underassessed or outdated genomic information. These risks have been explored and discussed in detail, particularly in *Williams v. Quest Diagnostics, Inc.*, a case that recently exposed the current and practical shortcomings to timely communication in genomic reanalysis.[2]

In *Williams v. Quest Diagnostics, Inc.*, which began in 2007, a child who suffered from seizures presented for clinical genomic testing. The laboratory that performed the test found a variant in the *SCN1A* gene, which it classified as a variant of unknown significance (VUS). There were two published reports at the time that identified this particular variant in a girl with Dravet syndrome. However, because the variant was classified as a VUS, the patient's doctors did not use the information in his care and continued to treat him with drugs that experts said were known to worsen seizures in patients with this condition. The family claimed this decision ultimately led to the patient's death.

As clinical genomic testing becomes more readily available, stories with similarly daunting consequences are likely to surface, exposing patients to avoidable harm and laboratories to potential liability. We believe timely genomic reanalysis could reduce the likelihood of such cases.

Our gene–disease and variant pathogenicity knowledge base is rapidly changing, and accumulating evidence demonstrates the clinical utility of genomic reanalysis for some medical conditions. For instance, one study showed that reanalysis of genomic sequence data in children with developmental disorders increased diagnostic yield by 13% compared with initial analysis. Genomic reanalysis also increased diagnostic yield of Mendelian disorders by around 10%.[3,4] Another study suggested increased diagnostic yields ranging between 10% and 21% after initial analysis for monogenic conditions.[5] Among 100 individuals in the MedSeq Project (50 with cardiomyopathy and 50 healthy), 22% received updated findings after genomic reanalysis (including new variants and/or updated variant classifications).[6] For hereditary cancer, variant reclassification occurred among 20% of patients[7] and the impact on clinical management was sometimes profound.[8] In many cases, patients with reported pathogenic/likely pathogenic variants, later downgraded to VUS, likely benign, or benign, had received years of unnecessary surveillance and underwent unneeded risk-reducing surgical intervention.[9] In addition, cascade testing misidentified those at risk for developing cancers, thereby altering the management across generations.[8]

These data add to the value of genomic reanalysis and support that it should become routine. Changes in the interpretation of clinical genomic test results are and should be expected as knowledge of gene–disease associations, as well as the population demand to understand these associations, continue to grow at unprecedented rates. Patients and their families, providers, and laboratories as stakeholders can benefit from timely genomic reanalysis due to a growing body of knowledge and evidence and to facilitate appropriate clinical care. However, our field should also acknowledge and consider the circumstances under which patients carry and manage any psychological, emotional, or practical burdens based on the uncertainty of diagnoses following an initial negative or uncertain report.

Clearly in some situations, it is critical for laboratories to inform clinicians of new variant interpretations to update disease management decisions. The implementation of routine genomic reanalysis would require a mechanism for laboratories to be paid for updating reports as well as better mechanisms to relay those reports to the physician and patient. For example, how can we scale routine genomic reanalysis in a sustainable fashion given the reality of financial constraints of most health-care systems? What are crucial elements to the successful clinical integration of genomic reanalysis? The ACMG statement recommends that clinical laboratories make concerted efforts to prioritize the reporting and communication of any reclassifications that may affect clinical management. But how should we prioritize genomic reanalysis to maximize the potential clinical impact without depleting the health system's budget?

The urgency to address these questions is exacerbated by (1) the rapidly increasing number of individuals who could be affected; tens of thousands of individuals have received genomic sequencing information through clinical or research channels, and programs including the All of Us program are poised to increase this number to over a million in the near

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future; (2) the large number of variants identified through the wider use of multigene testing and genome/exome sequencing; (3) advanced tools or bioinformatics systems that increasingly and more effectively identify variants of interest; and (4) advances in relevant medical knowledge associated with genes and variants.

Research is urgently needed to investigate implementation challenges to genomic reanalysis, such as logistical and communication challenges, informatics infrastructure required, and resource implications for implementing routine genomic reanalysis on a large scale in clinical practice. We also believe more research is warranted to identify the psychological and emotional challenges that might accompany genomic reanalysis in practice.

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