

Specific Aims

As genomic sequence data are being produced faster and at lower cost, the most significant challenge in clinical genetic testing today is variant interpretation, especially for ethnic and racial minorities for whom fewer reference data are available. Currently, there are marked differences in variant classification among clinical laboratories, with clinically significant discrepancies in 29% of variants interpreted (1, 2). Additionally, a substantial percentage of variants are classified as of unknown significance (VUS), with inadequate data to prove or disprove a pathogenic association with a medical condition. Progress already underway in interpreting genomic data will help ameliorate these problems. Factors driving improvements in the ability to reinterpret genomic variants include new ACMG guidelines for variant classification, efforts to develop expert consensus through ClinVar, growing amounts of genomic data in publicly available databases, and better computational methods to predict tolerance of genes to variation and to analyze sequence variants and predict pathogenicity.

Laboratories that conduct genomic sequencing will have to determine whether and when to apply this evolving knowledge to data from patients sequenced in the past. This issue will become even more pronounced for both diagnosis and risk prediction as clinical labs begin routinely sequencing larger panels of genes, whole exomes, and whole genomes in a growing number of patients. The federal Clinical Laboratory Improvement Amendments (CLIA) require laboratories to provide pertinent updates to clients when changes occur that affect test results or their classification (3, 4), but this has not been interpreted by most laboratories to mean that revised reports must be issued or that variants should be proactively reclassified. Absent definitive guidance from professional organizations or opinion leaders, the field seems uncertain how to respond. Stakeholders, including laboratories, providers, and patients, likely have different perspectives and opinions. Among the questions that need to be addressed are: Does a clinical lab have a responsibility to re-review and reinterpret genomic data? If so, how often should it do so? Should there be a limit to the duration of this responsibility? Does the obligation extend to all variant reclassifications or only those that may impact clinical decision making? To whom should reclassifications be reported? If reported to the ordering physician, what is the physician's or organization's responsibility to locate and recontact the patient? What if the patient is no longer under the ordering physician's care or is deceased? If the patient suffers an adverse outcome that might have been prevented with updated variant classification, who can be held legally responsible? Should recommendations differ for single variants and exomes/genomes? Should approaches differ for existing data from prior testing and future tests? It is the goal of this study to outline the challenges, consider the options, and offer recommendations for feasible approaches to variant reinterpretation.

To provide an empirical foundation for this critical discussion and develop guidance for the field, we will carry out a series of activities, each building on the prior ones. First, to provide guidance for the project, we will assemble an advisory panel of experts on medical genetics, clinical laboratory operations, insurance, health economics, regulatory and legal issues, and ethics, along with patient advocates. Then, we will conduct a series of focus groups with 3 key stakeholder groups: (1) directors of clinical laboratories that conduct genetic testing; (2) medical providers, including genetic professionals (medical geneticists and genetic counselors) and physicians from specialties that frequently order sequencing tests (oncologists, cardiologists, and neurologists); and (3) patients and parents of minor patients with personal and family histories of cancer, heart disease, and neurological conditions, who have undergone genetic testing in the past 5 years. Based on findings from the focus groups and after consultation with our expert panel, we will design and field a survey of the 3 stakeholder groups that will assess their positions on a range of issues related to variant reinterpretation. Finally, we will reconvene the expert panel to review the data and develop a set of options—specifying the advantages and disadvantages of each approach—and a final set of recommendations. The study's specific aims are:

Specific Aim 1: To conduct focus groups (16 groups; n=160) and surveys with three groups of key stakeholders—clinical laboratory directors (n=200); medical providers, including genetic professionals (n=600); and patients and parents of minor patients (n=600)—to investigate their perspectives regarding the practical, legal, regulatory, and ethical issues underpinning policy options for reinterpretation of genetic variants.

Specific Aim 2: To describe ethical and legal duties of laboratories and clinicians related to variant reinterpretation and model its economic impact, framing the resulting analyses to contribute to the development of normative recommendations.

Specific Aim 3: To integrate our empirical data and legal, ethical, and economic analyses to formulate a series of discussion papers, based on the findings of Aims 1 and 2, that outline the challenges, consider the options for resolution, and make recommendations for realistic approaches to the challenges of variant reinterpretation.