VIEWPOINT

Clinical Genomics
From Pathogenicity Claims to Quantitative Risk Estimates

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Fifteen years after the Human Genome Project, genomic variants have been associated with disease risk and outcomes in thousands of publications. Based largely on this literature, physicians who order genetic testing receive reports that indicate whether "pathogenic" variants have been found. This information aspires to form the basis of precision medicine. Knowledge of pathogenic variants is expected to lead to optimal management of individuals as well as their families through recommendations about further screening, prevention, and tailored treatment. However, in this Viewpoint, we suggest that current information on pathogenic variants is typically impossible to act on. This information is often unreliable and generally does not provide a quantitative measure of risk. The information the physician usually needs is the likelihood of disease among patients with the variant (penetrance), and an assessment of whether the genetic profile requires action or not.

The literature around pathogenicity is often conflicting. Different laboratories have discrepant classifications about which variants are pathogenic. Lack of consensus has generated disagreements and confusion about the clinical importance of different variants.[1] In response, the ClinGen resource, a recent $25 million investment into variant interpretation, has crowdsourced qualitative, categorical ratings of pathogenicity in the ClinVar database[1] to help diminish discrepancies in pathogenicity ratings. Even then, to make such information clinically useful, the long-term goal of understanding pathogenicity must be distinguished from the immediate goal of counseling a patient.

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Many pathogenicity claims may be too absolute and, when available, quantitative risk estimates are often exaggerated. For example, consider the iron-storage disease hemochromatosis. Variants in the *HFE* gene were once considered so informative they could be used to screen the general population; when the gene was studied in large populations, the chance that carriers expressed hemochromatosis was revised from more than 80% to less than 1%.[2] *BRCA* mutations have followed a similar trajectory, with repeated reductions in penetrance, and testing guidelines now vary considerably by ethnicity.[3] Moreover, large-scale exome data have reclassified hundreds of previously claimed pathogenic variants for the cardiomyopathies, ventricular tachycardia, X-linked intellectual disability, nonsyndromic hearing loss, and several other diseases.

These examples highlight a now common fate. Genetic variation thought to signify disease is often subsequently downgraded—pathogenic variation becomes of uncertain significance or even benign. If treatment decisions based on the variant are irreversible, such mistakes can cause harm. The statistical reasons that underlie overstated risks, particularly publication bias, selective reporting, winner's curse (overestimation of effects in initial studies), and population stratification, have been well documented for decades. They could be effectively solved by large consortia, standardized methods, data sharing, and integration of all available data in meta-analyses, as has been achieved by consortia performing genome-wide association studies for common genetic variants. These consortia have rarely arrived at pathogenic variants, but have instead focused on disease risk estimates.[4]

By contrast, the qualitative, yes/no pathogenicity concept lies at the core of the clinical application of genomics and is the usual figure of merit on positive testing reports received by physicians ordering genetic testing. A report of pathogenicity has major limitations for decision making. First, it is imprecise—how likely is a patient with a pathogenic variant to express disease? Second, it is coarse—2 distinct pathogenic variants need not convey the same disease risk. Third, it reduces a variant to a single role—a pathogenic variant may not be pathogenic in patients with a different genomic background and different nongenomic risk factors; the risk for disease and the need for treatment or other action may vary substantially across these patients.

Insisting on obtaining quantitative measures of disease risk for each variant still presents challenges. First, such measures are often subject to ascertainment bias—individuals who have their DNA sequenced are often not representative of the general population. Second, with movement to n-of-1 studies in precision medicine, many current statistical practices that have worked reasonably well in the setting of large population samples and common variants are inadequate to offer estimates of risk with any precision when it comes to solitary or rare observations. Third, historically, data both from patients receiving genetic testing as well as the general

Box. Desirable Aspects and Outcomes of Data Sharing to Quantify Pathogenicity Claims

Falsifiable: Assertions about variants that are not falsifiable (eg, a variant is pathogenic/linked mechanistically to hypertrophic cardiomyopathy) should be treated with caution

Responsible: Safeguards should be established to foster responsible data sharing between testing laboratories and investigators

Granular: Deidentified individual and family-level data with linked genotype and phenotype information would enable powerful reassessments of pathogenicity and measures of disease risk

Rich: To the extent that sufficient data for clinical stratifications such as age, sex, ethnicity, and comorbid conditions are available, stratified risk calculations can be undertaken

Communal: Using a shared underlying data source allows for controlled comparisons between different methods of identifying pathogenic variation

Actionable: Identification of a "pathogenic" variant that is "capable of causing disease" will often not inform clinical decision making

population have not been available to compare estimated disease risks in a systematic way. Fourth, whether this information, even if correct in providing accurate estimates of risk, is actionable is unknown (ie, whether changes in treatment or other management achieve better patient outcomes).

This picture has started shifting in recent years. Extensive sequencing data from large control populations are being used to systematically reexamine assertions about pathogenicity. There is also a growing statistical literature dealing with ascertainment bias, stratification, and uncommon outcomes in genetic association studies for rare genetic variation. These efforts are gradually helping improve variant classification in the medical literature. Yet the vast majority of clinical reports delivered to physicians to counsel patients today still lack any quantitative measure of disease risk.

To acquire precise disease risk estimates, resources could be devoted to sharing, contrasting, and combining deidentified patient-consented data from decades-old genetic testing practices. This is substantially different than sharing only high-level pathogenicity assertions, from which it is not possible to compute quantitative risk estimates via meta-analyses. Sharing the data underlying these assertions offers several advantages (**Box**). These data could be a substrate for transparent bottom-up approaches to develop disease risk estimates or more granular pathogenicity ratings for use by clinical genetic testing laboratories, researchers, and physicians. Privacy and cost are immediate concerns, but several successful examples of sharing sensitive data in federated, multi-institution networks are available that have at their core both transparency and local control of distributed data.[5]

Moreover, a shared information commons of primary genetic testing data from clinical genetic testing laboratories could counterbalance natural tendencies toward citation bias and deference to authority that might skew variant interpretation. If these data included at a minimum the variant identified, basic clinical information (presence or absence of disease or indication for testing), and demographic data, they could enable a new wave of pathogenicity reassessments and quantitative risk assessments. For conditions and diseases for which sufficient data become available, risk calculations can be stratified by comorbid conditions, ethnicity, and other clinically relevant variables and relevant nongenomic risk factors.

These and other efforts could drive clinical decision support to assist physicians at the point of care. It is likely that such standardized, collaborative team efforts will prove that many variants claimed to be pathogenic are not so, and even those that are pathogenic may not be actionable—nothing may need to change in disease management or preventive measures.[6]

Although some diseases are readily identified by pathognomonic findings, textbook examples, such as Koplik spots for measles, are the exceptions. Yet such extremes exist in much of genomic medicine: the typical scale dichotomizes variants as pathogenic or benign, with those not classifiable at either extreme of uncertain significance. The "pathogenomic" demand for causality, seemingly a higher ideal than correlation, is both misleading and constraining. Variation in the human genome is mostly suggestive, not definitive.

Instead of cementing the pathogenicity scale to resolve controversy or uncertainty, sharing the underlying data for those assertions may allow the community to develop more precise disease risk estimates and understand whether physicians should act on them (treat, manage, or advise the patient differently). In doing so, many stakeholders will likely benefit—genetic testing laboratories in benchmarking, researchers in pushing knowledge barriers forward, and most importantly, physicians and patients making treatment decisions using genetic variation information.

ARTICLE INFORMATION

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