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Genetic Variant Reinterpretation: Economic and Population Health Management Challenges

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The use of genetic testing for screening and treatment decisions for many health conditions is growing rapidly. There are thousands of genetic tests on the market today and common clinical domains include prenatal testing, pharmacogenetics, rare diseases, cancer diagnostics, treatment, and risk predictions.[1] Genetic testing includes panels of genes for a single clinical indication, such as breast cancer or cardiomyopathy, and genomic tests—including chromosome microarrays, exome and genome sequencing—largely for pediatric conditions such as intellectual disability, birth defects, and undiagnosed disorders. Genetic testing costs can range from $100 to $10,000 depending on the specific test.[2] Recent estimates suggest that the global genetic testing market will be valued at US$22 billion by 2024.[3]

Our understanding of the human genome is still in flux and for many human genetic variants we do not have enough information to know whether they are associated with disease (ie, pathogenic) or benign. These are classified as variants of uncertain significance. This means that many economic analyses and models of costs of diseases (eg, cancer) must be modified to include the possibility of reinterpretation over time as our understanding of a genetic variant changes. Expected future health care costs can increase or decrease depending on whether effective prevention is pursued. Other economic challenges include issues such as whether insurers should cover the costs of reinterpretation. Economic implications also differ for public and private insurance providers.

For genomic tests, the clinical yield of reanalysis of previously nondiagnostic exome sequencing about 1 to 3 years after initial testing can be as high as 23.1% because of the identification of new disease genes over time.[4] Changes over time in the interpretation of genetic variants means that a person who had a genetic test done 10 years ago could take the same test with the same lab today but receive a different interpretation of the same previously identified genetic variant. It is difficult to estimate precisely the cost of variant reinterpretation as it depends on the extent to which the data are organized to support reinterpretation and automation in a given laboratory. That is, the cost of variant reinterpretation includes work related to evidence review as well as work interpreting experimental/functional data. As far as we know, no systematic data exist on the costs of variant reinterpretation across laboratories.

For genetic testing, accurate and up-to-date variant interpretation is necessary to inform clinical decision-making for the physician, the patient and their family. Variant reinterpretation challenges become more pronounced as clinical labs sequence larger panels of genes, exomes, and genomes in a growing number of patients. As a result, variant reclassification raises important clinical, ethical, legal, and economic issues. This article discusses the economic and population health management implications of variant reinterpretation.

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Complexity of Variant Reinterpretation

The clinical, ethical, legal, and economic aspects of variant reinterpretation are important because a change in the risk of developing a given health condition may bring a shift in recommended health care. Variant reinterpretation also may provide new information that could affect family members and the health care services they do or do not need. Currently, it is unclear how the cost of reinterpretation can be incorporated into economic decision-making models as well as how it may influence payment and reimbursement options.

There are 2 primary pathways for reinterpretation. First, an initial genetic test may reveal an uncertain variant or may not identify any variants associated with a predisposition for a health condition. Reinterpretation done at a later point in time may reveal that a previously identified genetic variant is in fact associated with a medical condition or predisposition. This can be thought of as an initial false negative. Alternatively, although far less frequent, there may be a variant identified on the initial genetic test that is thought to be associated with a genetic predisposition for a health condition. Reinterpretation done at a later point in time may reveal that the genetic variant is no longer considered to be related to that medical condition or predisposition. This can be thought of as an initial false positive. If reinterpretation detects false positives, insurers may be more likely to cover the cost of reinterpretation. For false negatives, third-party payers may be less likely to want to pay for the reinterpretation because that would lead to higher future health care costs, although these actions also could lead to disease prevention or early diagnosis. However, in any given case, the presence and direction of changes in interpretation will not be known until the process is undertaken and the costs of reinterpretation are incurred.

Economic Considerations

The frequency of reinterpretation should be informed by the pace of increasing knowledge in variant pathogenicity, and this will vary by clinical indication. Furthermore, both the clinical and economic impact of reinterpretation should inform policies. Developing pragmatic coverage and reimbursement policies will thus be particularly challenging. For example, reinterpretation for a woman who initially was found to have a variant of uncertain significance for inherited breast cancer risk would be important within a time frame that is sufficient to prevent future disease. Yet, a patient receiving drug therapy that costs hundreds of thousands of dollars a year potentially could undergo reinterpretation periodically to detect false positives.

The complexity of assessing the clinical and economic value of reinterpretation suggests that decision-analytic policy models will be helpful in quantifying these outcomes and their associated uncertainty. Decision-analytic models are used by health care policy makers to assess value in health care technologies as well as to inform coverage and reimbursement policies. There also is a need to develop general guidelines that can be used to inform cost-effectiveness analysis of reinterpretation. Economic analyses to assess the adoption of new technologies rely on the use of structured economic models to assess the benefits and costs of adopting a given technology, understand complexity, assess impact over time, and evaluate the effects of a care process or treatment on different populations and health conditions. Thus, guidelines that can inform the development of economic models are needed to address issues such as how often variants are likely to be reinterpreted over time, what the expected cost impact of different treatment changes are, and what time horizon should be considered.

Disparities

Our understanding of the human genome is incomplete, particularly for individuals who are not of European ancestry given the available reference populations used to evaluate variants. This has potential consequences for health disparities. For example, the frequency of variants of uncertain significance in the *BRCA1/2* genes has been estimated to be 4.4% for Caucasians, 8.9% for African Americans, and 8.0% for Hispanics.[5] For larger panels of hereditary cancer genes, one laboratory has reported frequencies of variants of uncertain significance to be 22.1% for Caucasians, 30.3% for African Americans, and 24.9% for Hispanics.[6]

The main issue here is that the economic and health implications of reinterpretation may disproportionately impact populations with poorer health outcomes and a lower ability to pay. This would exacerbate health disparities and likely will be of interest to communities in which the impact could be relatively high (eg, states with large populations served by Medicaid).

Paying for Variant Reinterpretation

Variant reinterpretation also presents an important challenge when it comes to deciding who pays for the service to reassess genetic variants over time. For instance, providers with capitation payment arrangements with insurers may be considered to be responsible for covering reinterpretation costs as findings from variant reinterpretation could result in health care utilization pathways that are different from what was planned following the initial genomic test results. Payer coverage and reimbursement policies play a critical role in the adoption of new genomic technologies in clinical care because they provide the financial resources not only for testing but also for subsequent health care utilization associated with genetic testing. As such, the decision to pay for variant reinterpretation becomes particularly relevant because reinterpretation can lead to recommendations for health care treatments that were not considered to be necessary before results were made available, but were afterward.

The challenge of how to pay for variant reinterpretation is particularly significant in the United States given its highly fragmented health insurance market. Americans get their health insurance coverage from multiple sources (mostly Medicare, Medicaid, and employer-sponsored private insurance). A health insurer in the United States typically will offer multiple plans with different types of coverage, varying reimbursement rules, and different target patient populations. The US payer community is diffuse and it will be difficult to achieve consensus on a multifaceted issue such as reimbursement for variant reinterpretation.

The Need to Make the Case for Paying for Reinterpretation

Variant reinterpretation is likely to influence health care utilization in unexpected and highly unpredictable ways. Payers certainly will be unlikely to cover variant reinterpretation if its impact on health care utilization cannot be assessed over a reasonable period of time.

One approach that may prove useful to assess the case for variant reinterpretation is to think of the problem from the perspective of the budget impact on a payer, as insurers routinely consider the costs of new diagnostic or treatment approaches in their decision-making regarding coverage.[7] The costs of variant reinterpretation to a given payer, employer, or provider—though potentially large for certain subpopulations or individual patients—may have a small budget impact in a large population of covered lives if few people receive genetic testing and if few variants are of uncertain significance.

Budget impact analysis could be used to estimate the likely change in expenditures to a specific budget holder (eg, an employer) resulting from a decision to reimburse a new health care intervention at the population level. A budget impact analysis would measure the trade-offs over time between the costs of reinterpretation and the cost impact of potential savings associated with reinterpretation; for example, the savings associated with early detection and treatment.

Population Health Management Considerations

Genomic sequencing and variant reinterpretation are well aligned with different elements of population health management. Genetic testing can be congruent with patient-centered medical care models in the sense that this testing fosters patient autonomy, is consistent with treatment tailoring, requires team-based care, and empowers patients by providing them with information critical to various health care choices. There is evidence that screening the general population for a given gene mutation (eg, in *BRCA1/2*) may be more cost-effective than screening high-risk groups, such as people with a family history of a disease.[8]

Although there are efforts to integrate genomic information with clinical and environmental data (eg, the Healthy Nevada Project), the success of these initiatives hinges on understanding how variant reinterpretation may change the use of genetic data in population health management.[9] For example, interactions among genetic, clinical, and environmental information may affect cancer risk in particular ways but estimates of cancer risk may be highly sensitive to accurate variant interpretation.

Another important population health management consideration is that results of variants of uncertain significance in genetic testing are more frequent for ethnic and racial minority groups than whites.[10] Although many variants of uncertain significance are later reclassified as benign, clinicians may incorrectly manage these results the same way as pathogenic variants.[11] What this implies is that ethnic and racial minority populations may be more likely to receive inappropriate medical care given the differences in the frequency of variants of uncertain significance across different groups.

Lastly, the focus on big data and predictive analytics is evident in both genetic testing and population health management. There may be synergies in these 2 areas when it comes to how data are analyzed to understand health care utilization and better manage health care expenditures.

Next Steps

The use of genetic testing has been growing faster than our level of knowledge about genetic variants and their connection with health conditions at any given time. Genetic variant reinterpretation is becoming increasingly important to assess clinical care options — with patients, their families, clinicians, testing laboratories, payers, and policy makers all being interested in learning more about its clinical and financial consequences. Next steps that need to take place include the need for guidance to understand not only how often variants should be reinterpreted but also what is the financial impact of different treatment options and how different populations are affected. Close collaboration between all stakeholders is required to develop this guidance, which will be critical to develop a variant reinterpretation business case for payers. Moving forward will require an increased awareness about the economic challenges of genetic variant reinterpretation and holistic guidance on how to counter these challenges in order to maximize the value of genetic testing and match it with its speed of use in medical care.

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