

# Reimbursement for Genetic Variant Reinterpretation: Five Questions Payers Should Ask

David L. Veenstra, PharmD, PhD; John W. Rowe, MD; José A. Pagán, PhD; H. Shelton Brown, PhD; John E. Schneider, PhD; Avni Gupta, BDS, MPH; Sara M. Berger, MS, CGC; Wendy K. Chung, MD, PhD; and Paul S. Appelbaum, MD

**T**he advent of next-generation sequencing has enabled the generation and analysis of vast amounts of genomic data. Although technology has increased the diagnostic yield and efficiency of making genetic diagnoses, we also are presented with the challenge of not knowing what the clinical implications are for a significant portion of identified genetic variants, referred to as variants of uncertain significance (VUSs).

The good news is that with ongoing, very large genomic data sets and studies, every year we gain a better understanding of genetic variants. As a result, calls periodically arise for reinterpretation of available data to continuously identify new disease genes and disease-associated variants and more accurately assess genetic contributions to medical conditions.<sup>1</sup> This process—reevaluating the clinical implications of previously identified genetic variants—is referred to as genetic reinterpretation.

Genetic reinterpretation is important for US payers because medical care induced by reinterpretation could be costly, but, at the same time, reinterpretation can lead to improvements in patient outcomes and progress in equity across diverse patient populations.<sup>2</sup> However, the application of evidence-based processes for developing coverage and reimbursement policies for genetic reinterpretation will be challenging for several reasons. First, the determination of clinical relevance of a variant is based on multiple types of data and generally emerges over time based on scientific and clinical consensus. Second, the timing of reinterpretation will be highly dependent on the availability of new data, which will vary by clinical indication and patient population. Third, many payers likely do not have the expertise or resources needed to conduct such evaluations.

We propose a brief framework to facilitate the development of sound payer policies for genetic reinterpretation that identifies key issues and relies on organizations offering genetic reinterpretation services to provide evidence and rationale to support coverage of their services. The framework consists of 3 components: (1) types of genetic reinterpretation upon which to focus, (2) questions that should be asked of those offering reinterpretation, and (3) a process for requesting such information.

## TAKEAWAY POINTS

Continuing advances in genetic sequencing and large, ongoing studies have led to calls for periodic reinterpretation of patients' sequencing results.

- ▶ The development of transparent and systematic policies for coverage and reimbursement of genetic reinterpretation will be challenging.
- ▶ We propose a framework consisting of 3 components: (1) types of genetic reinterpretation upon which to focus, (2) questions that should be asked of those offering reinterpretation, and (3) a process for requesting such information.
- ▶ This framework will facilitate systematic and transparent policies for genetic reinterpretation in an efficient manner.

## Component 1. What to Focus on: Reclassification of VUSs to Pathogenic or Benign

The **Figure** shows the conceptual process of variant reinterpretation. Results from genetic tests fall into 3 major categories: (1) pathogenic/likely pathogenic ("pathogenic"); (2) benign/likely benign ("benign"); and (3) VUSs. By far, most variants are benign. VUSs, however, are not uncommon. The assessment of VUS arises when family, epidemiological, or functional studies provide insufficient evidence to determine if the variant is associated with disease risk.

Although there are many possible types of variant reclassifications, the most likely result of accumulating evidence is the most obvious: making uncertain variants more certain—that is, reclassifying them as benign or pathogenic. Although the specific number varies based on date of the study and type of testing, the vast majority of VUSs will be reclassified as benign but perhaps 15% of VUSs will be reclassified as pathogenic.<sup>3-6</sup> From a pragmatic perspective, it thus makes the most sense to focus on the impact of the reinterpretation process on these 2 types of reinterpretation: VUS to benign and VUS to pathogenic.

## Component 2. What Are the Key Data Elements? Five Questions to Ask

Next, we rely on a decision-analytic approach to conceptualize and identify key data and outcomes given the lack of direct evidence

from sources such as randomized controlled trials.<sup>7</sup> The intervention in this case—reinterpretation—would be compared with a scenario in which reinterpretation is not conducted. We are thus interested in incremental outcomes. Baseline risk and treatment effect size are the metrics we typically consider when evaluating health care interventions. In this case, baseline risk is analogous to the prevalence of pathogenic variants, and the effect size is driven by frequency of reclassification as well as the downstream clinical and economic impacts. The cost of the intervention is of course important. Lastly, uncertainty and heterogeneity of effects across patient populations must be considered.

**Question 1. How often would sufficient evidence accumulate to reclassify VUSs across clinical applications?** An estimate of the frequency of reclassifying VUSs is essential, as it will be one of the primary drivers of clinical and economic value. Given the diversity of genomic findings, it may make the most sense to focus on high-volume tests that are medically actionable, such as testing for hereditary cancer syndromes and cardiac disease.<sup>8</sup> Conditions for which a molecular/targeted treatment is available, effective, and likely expensive also merit scrutiny.

Drivers for reclassification will be large releases of new reference data, new functional experiments, new publications of disease genes, and improvements in prediction algorithms.

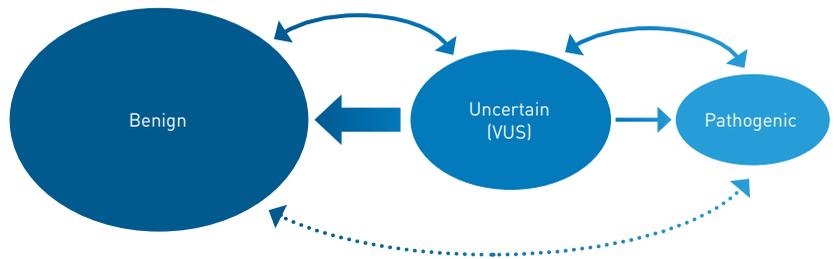
**Question 2. What are the clinical consequences of variant reclassification?** Recommendations for clinicians encourage them not to make medical decisions based on a VUS because the clinical significance is uncertain. Yet clinicians may be tempted to act, both from a desire to help their patients and potentially because of liability concerns.<sup>9</sup> VUSs also may lead to worry for patients.<sup>10</sup>

Reclassification of a VUS to pathogenic can trigger medical decisions based on that genetic diagnosis, initiate cascade screening in family members, and influence family planning decisions. Medical actions should be supported by guidelines to increase clinical utility and likelihood of reimbursement.<sup>11</sup>

Reclassification of a VUS to benign should not trigger additional medical decisions but will resolve the uncertain status of the VUS that was identified, potentially alleviating patient worry. Furthermore, any unnecessary actions that were undertaken that could have associated clinical risk (eg, more frequent colonoscopies) could be stopped.

**Question 3. What are the economic consequences of variant reclassification?** Reclassification of VUSs could lead to either an increase or a decrease in health care spending. Because reclassification to benign will be most common, the potential cost savings from avoiding nonindicated health care, including ongoing monitoring, in these patients may offset the cost of indicated health care in cases of reclassification to pathogenic.

**FIGURE.** Conceptual Process of Variant Reinterpretation\*



VUS, variant of uncertain significance.

\*The sizes of the circles approximate the relative frequency of 3 types of findings. The arrows represent possible reinterpretation outcomes that can lead to variant reclassification; the width of the arrows represents relative frequency; the dashed line indicates very low frequency.

Importantly, the costs saved by reducing downstream adverse health outcomes such as the development or progression of disease should be considered, as well as impacts on accurate risk stratification of family members with appropriate use of cascade genetic testing once a pathogenic variant is identified in the family.

**Question 4. How much does reinterpretation cost, and what is the model for the service?** The steps to providing reinterpretation include (1) building a genomic data warehouse, (2) adopting a pipeline for automated variant reassessment, (3) human review of any flagged variant, and (4) issuing a revised report. This process will have a large, fixed cost initially to build the infrastructure, with a small marginal cost for future reinterpretations. For example, reanalysis can be triggered by a laboratory seeing the same variant in another patient and classifying it differently. In this case, the primary cost is to recontact the referring provider.

Reimbursement for chronic disease management may provide a useful model for the structure of a reimbursement contract. A payer could go to multiple laboratories and contract for a certain number of reinterpretations. Another consideration is that with dropping sequencing costs, reinterpretation over a limited amount of time could be included in sequencing cost or provided as an ongoing subscription service.<sup>12</sup>

**Question 5. How heterogeneous is the yield of variant reinterpretation across diverse clinical populations?** Ancestrally underrepresented groups are less likely to benefit from current genetic testing because a large amount of genetic reference data involves individuals of European ancestry, and these findings are not generalizable to minority groups.<sup>13-16</sup> Thus, minority populations are more likely to receive VUS results. However, as reference data sets improve, minority populations are the most likely to benefit immediately from reinterpretation because common variants in these ancestral groups can quickly be discarded as causes of rare diseases as they will be present in large numbers of individuals.

### Component 3. Payers Request Evidence and Rationale From Reinterpretation Providers

Finally, we propose that rather than undertaking the task of assessing genomic reinterpretation on their own, payers place the onus of providing information on those seeking reimbursement for such services, namely laboratories that perform genetic testing. This approach follows the conceptual process and format established by the Academy of Managed Care Pharmacy for the submission of evidence from drug and biologic manufacturers to support formulary listing.<sup>17</sup> Although many differences exist between assessment of pharmaceuticals and variant reinterpretation, the concept is similar: Provide guidance for important evidence that improves communication between laboratories and payers and enables payers to make structured, informed decisions.

### Conclusions

There are unresolved issues related to genetic reinterpretation, such as who should decide if and when reinterpretation is needed, who should perform the reinterpretation, and who should be informed about the results. It is not yet clear what the responsibilities and roles of laboratories, geneticists, clinicians, patients, payers, and policy makers are in handling these issues.

Health care payers can do their part to help address these challenges by using a systematic and transparent approach to coverage of genetic reinterpretation. Relying on the concepts outlined here and evidence and rationale from genetic sequencing providers will facilitate this goal in an efficient manner. ■

**Author Affiliations:** The Comparative Health Outcomes, Policy & Economics (CHOICE) Institute, School of Pharmacy, University of Washington (DLV), Seattle, WA; Department of Health Policy and Management, Mailman School of Public Health, Columbia University (JWR), New York, NY; Department of Public Health Policy and Management, School of Global Public Health, New York University (JAP, AG), New York, NY; School of Public Health in Austin, The University of Texas Health Science Center at Houston (HSB), Austin, TX; Avalon Health Economics LLC (JES), Morristown, NJ; Division of Clinical Genetics, NewYork-Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center (SMB), New York, NY; Kennedy Family Professor of Pediatrics in Medicine, Division of Clinical Genetics, Department of Pediatrics, Columbia University (WKC), New York, NY; Department of Psychiatry, Columbia University Vagelos College of Physicians and Surgeons, NY State Psychiatric Institute (PSA), New York, NY.

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**Address Correspondence to:** David L. Veenstra, PharmD, PhD, Comparative Health Outcomes, Policy & Economics (CHOICE) Institute, School of Pharmacy, University of Washington, Box 357630, H375 Health Science Bldg, Seattle, WA 98195-7630. Email: veenstra@uw.edu.

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