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Overcoming Barriers to Genomic Medicine Implementation

Article:
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Guest: Dr. Heidi Rehm from the Center for Genomic Medicine at Massachusetts General Hospital, the Program in Medical and Population Genetics at the Broad Institute, and Broad Clinical Laboratories.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Since the completion of the Human Genome Project in 2003, genomic testing has revolutionized the practice of medicine, facilitating advances in patient care that would have seemed the realm of science fiction just a few years ago. Yet despite these advances, clinical genomics has tremendous untapped potential to further improve outcomes but is being held back by several barriers.

First, genetic testing is widely underused due to poor reimbursement, depriving many patients of potential benefit due to financial constraints. Second, patients who do undergo testing are often confronted by variants of uncertain significance [VUS]. Are these variants responsible for the patient's symptoms or simply benign sequence changes? Third, genomic data often live in different databases, making it difficult to compile sufficient cases to confidently characterize a variant or associate a novel gene with an inherited condition. Fourth, individuals of non-European ancestry are disproportionately underrepresented in most existing databases, making it difficult to identify common variants in these non-European ethnic groups.

A new reflection article, appearing in the January 2025 Genomics special issue of *Clinical Chemistry,* highlights these barriers preventing further advances in genomic medicine, and proposes structural solutions to make them a thing of the past.

In this podcast, we are joined by the article's author. Dr. Heidi Rehm is an investigator in the Center for Genomic Medicine at Massachusetts General Hospital, Co-Director of the Program in Medical and Population Genetics at the Broad Institute, as well as the Medical Director at Broad Clinical Laboratories. She is a principal investigator of ClinGen and gnomAD, providing resources to support the interpretation of genes and variants. So, Dr. Rehm, what are the most common uses of genetics in medical practice today, right now?

Heidi Rehm: So, genetics is used in a lot of different areas of medical practice. I would say the most common ones today are in diagnosis of rare diseases. So, a patient has symptoms that suggest that they may have a genetic cause and genetic testing is ordered to try to identify a cause of those symptoms. Another major area of use is in tumor testing to guide treatment. So, a lot of patients with cancer will have their tumors assessed by genetics in order to inform their treatment plan.

These are probably the two most common ways that genetics is used today. Also, increasing use in more preventive arenas. Carrier screening is certainly a widely and very common application of genetic testing, as well as increasingly, risk for cancer based on family history or other concerns, and then even starting to use it more in infectious disease and also pharmacogenomics. But those aren't quite as widely used as the rare disease and cancer arenas.

Bob Barrett: What are some challenges in implementing universal reproductive carrier screening?

Heidi Rehm: I mentioned that genetic testing for carrier screening is common. I think some of the challenges that we deal with are that there's not enough education around the importance of this to think about before you get pregnant. I believe it's about two-thirds of all patients who are offered carrier screening are offered it after they become pregnant. And that then narrows the options for how an individual might use that information if they're already pregnant. It also creates a pretty urgent timeline for getting information and allowing families to make choices. So I think that's one of the biggest implementation challenges is "how do we move carrier screening to preconception and have it addressed before an individual becomes pregnant so that they can think about it in the context of family planning and make decisions that are most consistent with their own choices?" But that is definitely one of the bigger challenges is have this be a common question that's asked during primary care visits, things like "are you planning to get pregnant anytime in the next year?" so that those discussions can happen and the opportunity to consider carrier screening before pregnancy happen then.

Bob Barrett: What are some of the benefits and some of the drawbacks of the use of multigene panels versus exomes or genomes for genetic diagnosis?

Heidi Rehm: Yeah, I think some of the challenges when we think about what's the right test. Sometimes the patient has a very defined phenotype and it's pretty easy to pick the right test for that. Those clinical symptoms or phenotype, let's say it was the patient has hearing loss.

That's a pretty well-defined phenotype, and you can order a panel test and usually those tests are pretty comprehensive to include all the genes because it's easy to say this is a hearing loss gene or not. However, there are other phenotypes that are more complex. A lot of the neurodevelopmental phenotypes that may involve more non-specific features like intellectual disability, microcephaly, macrocephaly, epilepsy, failure to thrive, you know, other forms of developmental delay. And these can be much more non-specific features that make it hard to point to a specific condition, and then figuring out what panel to order can be challenging.

In addition, it's pretty common that phenotype or the patient's clinical symptoms are not given to the lab during panel-based testing. And the labs really simply evaluate every variant in that panel and give a list of what's pathogenic or uncertain back to the physician without consideration for is/are one of these variants an actual reasonable match for the patient's symptoms. And that part of the diagnostic process doesn't happen as comprehensively. In comparison for an exome or a genome, you're looking at everything in the genome. You can't interpret it without the physician providing pretty detailed phenotype clinical symptoms.

And so, those interpretations can be much more specific and directed in an exome or genome than they can in a panel where the phenotype may be much less specific, and you need the judgment of the laboratory geneticist to guide what gets put on the report. So, in fact, we've found that the rate of VUSs getting returned for genetic tests is actually higher in panels, even though there are fewer variants being identified. And that is because no one is using professional judgment to decide which variants from a panel should get reported based on the patient's phenotype. Whereas, that does happen in exome and genome sequencing.

Another factor is thinking about reanalysis. New genes get discovered all the time. Patients' clinical symptoms evolve over time. And if you've done an exome or genome, you can go back and reanalyze it to look for new results that might represent new genomic knowledge or understanding new patient symptoms to reassess that. Whereas, for a panel, you're often stuck with the genes that you first looked at. So, I think these are a lot of factors and they're leading us to move more and more towards exome and genome because of the benefits of that more directed, clinically guided interpretation, as well as the ability to reanalyze over time.

Bob Barrett: Getting an inconclusive test result. It's challenging for both patients and physicians. How are we tackling this problem?

Heidi Rehm: So it is definitely a challenge. About a third of all genetic tests get an inconclusive result due to a variant of uncertain significance. In this case, I'm talking about what we call diagnostic testing, where the patient has symptoms and you're trying to find an explanation. And in those cases, a third of reports end with a VUS as the only answer. That's challenging. So, how are we trying to tackle this problem in medical care, in genetics?

There're a few different ways we're doing this. One is developing new guidelines for the interpretation of genetic variants. And those new guidelines, in terms of the piloting that we're doing with them, they're not out yet, but they're being developed in ways that make it a little easier to get variants into the likely benign category, as well as a little easier to get them to pathogenic when the right evidence is there. And so, we actually think that the fraction of variants that get classified as VUS will go down with the new guidelines.

The other thing we are pushing out is a natural subdivision of VUSs based on the new guidelines. This will be automatically calculated based on how the new guidelines are and they will put variants into subclasses, the VUS high, VUS mid, and VUS low. And those categories then correlate with the likelihood that variant will become likely pathogenic or will become likely benign. And so, this will help guide physicians and even patients to decide how much energy to put on to monitoring a variant of uncertain significance or following up on it.

If it's VUS high, it's got a much higher likelihood of becoming pathogenic in the future, and pursuing, and other studies monitoring those variants over time will be important. In contrast, a VUS low from some other data that we put together, we almost never see these variants move up to pathogenic. And as such, we can guide physicians and patients to put less emphasis on monitoring or intervening with respect to those variants. So, in this way we can help reduce the negative impact of getting these uncertain results back and really help guide the clinician in the appropriate follow up.

And then lastly, there's more exciting research and approaches to determine the functional impact of variation through large scale assays, sometimes called MAVE, or multiplex assays of variant effect. And so, we believe that there will be better ways to evaluate many of these variants that we don't understand today with large scale research studies, and that will help reduce the number of variants that fall into this category in general.

So, with all these things, we hope over time and in the coming years that this will be a much less negatively impactful area of genetics.

Bob Barrett: So, in the coming years, what advances in the field are needed to scale genomic interpretation?

Heidi Rehm: I think one of the most important aspects of thinking about the scale of genetic interpretation is really about data sharing. These variants are often incredibly rare. Most variants, over three quarters of the variants that have been submitted to ClinVar have come from one lab, likely because they were only seen in one patient ever. That's millions of variants. And so, it just highlights how rare these variants are. And if we are to amass information on these variants and be able to understand them, it's going to take global data sharing, so that we're sharing who a variant has been observed in, what their phenotype was, whether other evidence was generated on that variant, be it clinical studies or functional studies, experimental results. But these results and these types of evidence need to be shared broadly across our community, so that whenever a variant is identified on a patient, we have ready access to all of the knowledge and information about that variant. And that kind of large-scale data sharing, as well as some of my comments about scaling the functional interpretation of variation, is going to help us really scale the interpretation of genetics.

Also, making sure every gene and every variant are associated with an understanding of what disease is associated to that gene or that variant, and being able to collect this information through large scale clinical databases of patient information is really going to help drive the automated and scalable interpretation of genomes for individuals. But that's going to take commitment and infrastructure from our community to really help drive that.

Bob Barrett: So what does the future hold for genomic medicine? How will we use genomics in everyday practice in five or ten years?

Heidi Rehm: I think over the years, we will move towards an arena where we think about the genome as a component of our health, of ourselves. And it's not a single test to answer a single question, but more a resource that we have about ourselves that can be used to inform much of our care. So, you can imagine at the earliest stage of an individual's life that could even be fetal development, obtaining the genome of an individual and then using that to help guide decision making. That decision making could be to identify risk for disease in the future so that you can intervene and prevent downstream adverse events. Could be guiding which drugs should be used and the dosage of those drugs. In terms of

pharmacogenomics, helping guide the treatment of individuals with disorders.

It could also be used to diagnose the moment symptoms arise. If I have chest pain and I get an echo and see a thickened heart wall, we can immediately look at the genome and say, "what variants might relate to a thickened heart wall?" and help in real time inform the care of a patient, even in the emergency room. So, I think really in the future we'll see the genome as really a part of many aspects of the care of an individual, helping decide what drugs, what dose, how to interpret symptoms and identify risks for disease that we can intervene and prevent in the future. And that's how I hope to see genomic medicine operating in the future.

Bob Barrett: Well, finally, Dr. Rehm, how can we ensure equity in how our population benefits from genomic medicine?

Heidi Rehm: Equity is really important in thinking about all aspects of medicine and certainly genetics. We have found that the ability to diagnose the cause of disease in a patient is diminished in those individuals who are underrepresented in populations. And the reason for that is they haven't been enrolled in the same research studies or been given access to the same clinical care. And so, the knowledge that we can generate on those individuals has been diminished, and that reduces the likelihood that we obtain an answer for their symptoms.

Similarly, the ability to get rid of VUS is also related to how much population data we have on individuals from their similar background, and we haven't historically had a lot of data from individuals of underrepresented backgrounds. So, in order to in the future make genomic medicine accessible to all in an equitable manner, we have to ensure that all of our research studies enroll all populations and are studying the variants that we identify in those populations. We also have to ensure that health care access is equitable so that when we are offering genetic testing, all individuals are benefiting from those tests. They're getting referred to specialists appropriately. They're being considered for preventive genomic medicine, and all aspects of genetic care are offered equally, and that will enable us to really have an equitable environment for offering genomic medicine.

Bob Barrett: That was Dr. Heidi Rehm from Massachusetts General Hospital in Boston, Massachusetts. She wrote a new reflection article on "Overcoming Barriers to Genomic Medicine Implementation" in the January 2025 special issue of *Clinical Chemistry*, and she's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.