Clinical Utility and Long-Term Feasibility of Exome and Genome Reanalysis: From the Perspectives of a Clinical Laboratory

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Guests: Dr. Jenny Ji from the Department of Pathology and Laboratory Medicine at Children's Hospital Los Angeles and Dr. Marco Leung from the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital in Columbus, Ohio.

Randye Kaye: Hello, and welcome to this edition of *JALM* Talk from *The Journal of Applied Laboratory Medicine*, a publication of the Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye.

Unlike many other clinical laboratory tests, clinical exome and genome sequencing are typically thought of as once-in-a-lifetime tests, since the patient's germline genome will not change over time. However, inevitable updates to published data and population and disease databases may allow for changes in the interpretation of previously sequenced data over time. This concept is referred to as reanalysis of genomic data, and it may increase diagnostic yield, allowing for improved understanding of the underlying disease for some patients. However, reanalysis is not always appropriate and there are uncertainties for this process such as when and how to conduct a reanalysis.

The January 2024 special issue of *JALM,* entitled "Molecular Testing in Medical Practice: Challenges and Triumphs of the Genomic Age," features an opinion article that discusses the clinical utility and long-term feasibility of exome and genome reanalysis from the perspective of the clinical laboratory. The authors also discuss regulatory considerations and issues of patient consent and test reimbursement. Today, we're joined by both authors of the article. Dr. Jenny Ji is a clinical laboratory director at the Clinical Genomics Laboratory in the Department of Pathology and Laboratory Medicine at Children's Hospital Los Angeles. Her primary interests are in molecular diagnosis of rare genetic disorders and pediatric brain tumors. Dr. Marco Leung is a clinical director at the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital. His research interests are in the development and implementation of molecular assays for germline and somatic diseases. Welcome Drs. Ji and Leung.

Dr. Ji, let's begin with you. In the article, you mentioned that reanalysis could potentially generate new diagnoses, but that

the diagnostic yield from reanalysis can vary and may even decline over time. Could you elaborate on this?

Jenny Ji: Absolutely. I will begin by talking about why we might find a new molecular diagnosis when we take another look at the exome or genome sequencing data after a period of time. So in the world of genomic medicine, we have really seen significant advancements in the past decade, especially in the discovery of new disease associated genes by advanced technologies. There may be new published literature out there describing novel disease genes, variants with updated functional data, and even additional clinical information that can broaden our understanding of the diseases. All of this can give us a new perspective on the genomic data and the knowledge may not have existed during the initial analysis.

Sometimes we might get new information about additional family members, and that can help us figure out how the disease is inherited in the family. We look into whether the identified variant is inherited or de novo, and if the family members who have the variant show the same phenotype and this help us to see if there is a connection between the variant we found and the clinical features of the family members. And sometimes the patient's clinical features change over the time and these updates can give us additional clues to identify a genetic cause. Also, our informatics is advancing as well. There are certain types of variants that require a better pipeline to be identified, and these variants may not have been called during the initial analysis.

And lastly, but importantly, with more and more large-scale genomic sequencing, we now have extensive genetic databases, including both disease gene variant databases and population databases. And these resources are really helpful for us to interpret the variant better or more accurately, and these resources may not have been available during the initial analysis. Now, in terms of the diagnostic yield, we have early studies suggested that exome reanalysis leads to about 5 to 10% increase in diagnostic yield. But this yield can vary and even decline over time and there are several factors that may contribute to this variability.

We have just talked about how new gene disease discovery could result in new diagnosis, but when the pace of new gene discovery slows down, the yield of the reanalysis may decrease. And also the quality of the initial exome or genome analysis is really getting better and better. So expectedly, reanalysis of these data may not increase the diagnostic yield.

Also, in recent years, there is a bigger focus on family-based analysis rather than only analyzing the individuals with the clinical features. And in these cases, the diagnostic yield has

already been maximized. And of course, when reanalysis referrals increase, especially the time gap between the initial analysis and reanalysis is shortened, the yield is expected to drop. So ultimately, I think the success of reanalysis really depends on whether the molecular diagnosis lies within the existing exome or genome data. Are the tools good enough at the detection of specific variant types? Do we know enough or have sufficient knowledge to interpret the identified variant? And whether reanalysis is the right approach for a specific case? And all of these contribute to the diagnostic yield.

Randye Kaye: I see. Thank you. Dr. Leung, how do you address the perspectives of a clinical laboratory in relation to the utilization of exome and genome reanalysis? What are some specific considerations for laboratories implementing these practices?

Marco Leung: Yes, so there are a few aspects that laboratories would need to consider when they are implementing exome or genome sequencing reanalysis, and I can give you a few examples. One is the new consent required for reanalysis. The lab would have to determine whether their original consent for the initial exome or genome sequencing actually cover data reanalysis or not. And if they're not covered, the lab would need to acquire a new consent for the reanalysis.

Another aspect they have to consider is what kind of reanalysis would the lab offer? Is it just reclassifying a single or subset of reported variants, or is the whole case being reanalyzed? And also, if the original data metrics, such as coverage depth and coverage breadth, do not meet the laboratory's current threshold, would the lab consider reprepping and resequencing the sample again? Another consideration is whether the lab would use the same reporting criteria for reanalyzed cases as they do for initial analysis. So these are just a few examples of decision points that laboratories should consider when they're implementing reanalysis, and these processes should be listed and documented in the SOP.

Randye Kaye: All right, thank you. Can we talk about long-term feasibility of reanalysis? Dr. Ji, what are the challenges and considerations regarding the implementation and sustainability of exome and genome reanalysis in clinical practice?

Jenny Ji: Definitely. As genomic testing becomes more and more widely used, it's really important to think about the long-term sustainability of exome and genome sequencing reanalysis from the lab's standpoint. One big challenge is dealing with this huge amount of data, it's like piling up really fast. So clinical labs need to invest in computing infrastructure and

robust data management systems to handle it all and this investment can be both costly and challenging to maintain. And also, we are dealing with genomic information. Making sure it's safe and secure is also a big deal.

Now, the cost of sequencing is dropping, but the amount of testing and data we are dealing with is increasing, so reanalyzing old genomic data might start looking different in the future. Maybe we'll just resequencing instead of going through the traditional reanalysis in the future. Another challenge is finding the highly trained personnel who are proficient in such tasks because it involves complex processes. It's not just having people. The complexity of reanalysis really demands a specialized workforce with expertise. They got to know not only clinical genetics and genomics, but also clinical bioinformatics, clinical lab procedures and regulations. And so maintaining a skilled genetics team is really important for the long-term success of reanalysis.

And also, we all know that interpreting genomic data, especially when it comes to reclassifying variants, it's still a big challenge. And Dr. Leung just mentioned that the type of reanalysis can be really complex. It has multiple types from reanalyzing a single variant, multiple variants, or an entire case. So it's really complex even to choose which one of these options to proceed for a particular case. So I strongly believe that collaboration between clinical laboratories and clinicians is really critical for its success. And lastly, since reanalysis can be labor intensive and can involve a lot of manual work, so introducing more automation is important. Ideally, we'll have a system that automatically highlights changes in the existing data set and updates things accordingly. It might not solve all the problems, but it could take a load off and make the whole process smoother. The challenge is that the automation itself can be complex and could take a long time. So these are the most common challenges of exome and genome reanalysis in clinical practice.

Randye Kaye: Thank you. I have one final question. I'll give this to you, Dr. Leung. How does the current reimbursement landscape accommodate the need for exome and genome reanalysis in diagnostic processes? Are there any specific challenges or considerations that impact reimbursement policies for these genetic testing methods?

Marco Leung: Yes. For the reimbursement for exome and genome sequencing reanalysis remains to be very challenging, even though this is just a "reanalysis test." Like Jenny mentioned earlier, the processes are actually quite complex, labor intensive, and costly, especially when specialized informatics expertise and computational resources are required. The cost

for reanalysis can actually be quite substantial. However, the reimbursement for reanalysis remains very abysmal. I would say that in the last couple of years, there have been a lot of reanalysis studies demonstrating the diagnostic improvements and hopefully with this increasing number of reanalysis study, it will be convincing enough to change the insurance policy leading to better reimbursement.

Randye Kaye: All right, thank you so much. Very interesting topic, and a lot of information. Thank you for joining us today.

Marco Leung: Thank you.

Jenny Ji: Thank you for having us.

Randye Kaye: That was Drs. Jianling Ji and Marco Leung discussing their opinion article, "Clinical Utility and Long-Term Feasibility of Exome and Genome Reanalysis: From the Perspectives of a Clinical Laboratory." This article is from the January 2024 special issue of *JALM,* entitled "Molecular Testing in Medical Practice, Challenges and Triumphs of the Genomic Age." Thanks for tuning into this episode of *JALM* Talk. See you next time. And don't forget to submit something for us to talk about.