GIM/GIMO

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Implementation of Genomic Medicine - Bridging the Gap Between Promise and Practice

Genomic medicine has evolved from simple tests to rapidly growing applications of whole genome sequencing. Despite enormous technical advancements, the translation to routine clinical practice remains incomplete. Dr. Funke's talk will provide an overview as well as concrete examples of critical remaining and newly emerging challenges that need to be addressed. Drawing from her involvement in numerous expert-led efforts over the last 20 years, Dr. Funke will discuss a range of representative challenges including the gap between regulatory requirements and availability of suitable test implementation resources, the need to rethink delivery of professional test development guidance to the clinical laboratory workforce, addressing educational gaps as applications begin to include proactive testing of healthy individuals, and the importance of unifying nomenclature to enable seamless communication of genomic test results across diverse stakeholder communities.

Supported by Illumina, the webinar featured speaker:

Birgit Funke, PhD
Clinical Laboratory Director/Consultant, Shriners Children's Genomics Institute

Moderator
Dr. Lauren Massingham, MD, FACMG
Director, Clinical Genetics, Boston Children's Hospital

Below are questions from the webinar's Q&A session.

1. **Although not regulated from the lab end, when providing whole genome sequencing interpretations instead of providers, may you comment on the requirements for CLIA/ISO certifications?**

   I am afraid, am not familiar enough with ISO certification requirements! For CLIA, there is no single CLIA regulation that explicitly states, "variant interpretation is part of the testing process." The reason being that CLIA was written long before the practice of variant interpretation became part of what testing laboratories do. It is somewhat implied that classification is performed prior to report sign-out, but not regulated (e.g., via proficiency testing). CAP is more "up to date" and does have specific requirements (such as "MOL.36155") and does offer a few PT challenges that include elements of interpretation. In my opinion, a responsible lab director absolutely needs to ensure competency and accuracy of variant classification, and while it would technically be possible (if a lab were just CLIA regulated) to issue a report with just the raw variant call, this would not fly with ordering providers. In summary, my intent was to point out that practice has evolved to include this service, but regulations are not sufficiently caught up to enforce good practice.

2. **Can you address in a few words your philosophy on how you like to deal with sequencing errors and the importance of controls?**

   Absolutely! I am a bit of a "hardliner" when it comes to this topic. At least in a germline testing setting. There is often tremendous pressure to bring tests to the market fast, and many labs rush through validation studies, where one is supposed to develop well-founded measures of accuracy, especially for false positive results. Every technology has them, and one can either optimize the technology further or use orthogonal variant confirmation to rule out false positives. One usually ends up needing some level of confirmation, but it can be minimized if the test is robustly developed and benchmarking controls such as the NIST controls are used throughout development. NYS and CAP have relatively clear guidance on this, with NYS being very specific on when confirmation is no longer necessary. CAP is (as always) more permissive but does state that the lab must have studies justifying that confirmation is not necessary.

3. **Sanger sequence, please explain.**

   I am not sure if this is a missing part of the question!

Sanger sequencing is the "first generation" sequencing technology that reads one DNA fragment at a time, producing highly accurate sequences up to about 1,000 base pairs long. It's relatively slow and expensive for large-scale projects, making it best suited for sequencing individual genes or verifying specific DNA segments.

Next-generation sequencing (NGS) can simultaneously sequence millions to billions of DNA fragments in parallel, making it much faster and more cost-effective for analyzing entire genomes or large numbers of samples. While individual NGS reads are shorter and slightly less accurate than Sanger sequencing, the massive parallel processing and high coverage depth compensate for this, enabling applications like whole-genome sequencing, RNA analysis, and population studies that would be impractical with Sanger methods.

Sanger sequencing continues to be used, however, less as a primary sequencing method, but more for confirming variant calls obtained through NGS (as this does have a higher error rate)

4. **Does using a single human reference compromise variant detection and equity across ancestries, and should clinical pipelines transition to a pangenome reference?**

   This is an excellent and timely question that touches on a critical issue in genomics! I do not have actual experience with using pangenome references, but based on what I read, there is no doubt that it will dramatically improve variant detection in ancestries that are not well represented in the current reference sequence. That seems to be especially true for complex structural variants and of course, is tightly linked to the use of short-read sequencing technologies that are inherently more challenging when it comes to accurate alignment. Smaller variants are easier to detect in general, but when reads from an underrepresented ancestry have too many (benign) variants that differ from GRCh37/38, reads may not align at all, and if they also contain a pathogenic variant, this could be missed.

5. **What is your recommendation for labs starting from scratch for WGS?**

   I highly encourage labs starting from scratch to invest into WGS. The laboratory workflow is much simpler than capture-based sequencing, and therefore, data quality tends to be higher (this is especially true for CNV detection). It is often still argued that it remains more expensive than older approaches. While that is true at first glance, one should invest time in expanding the usual COGS analysis beyond the basic WGS lab process only. Once you layer on things like standardizing the lab workflow (you can run all tests ranging from genotyping to sequencing panels to true

WGS), the ability to re-analyze the data, etc., the equation will start to be more convincing. Additionally, it is clear now that the price will continue to drop fast, and if you start from scratch now with an already outdated approach, you will need to budget for migrating to WGS very soon, which will add tremendous development and validation costs.

6. **Thank you for the excellent presentation. Clinical question, the somatic testing in HRD/HRR in ovarian/prostate cancers for mutations for the use of PARP inhibitors. If the HRD and HRR are negative, should we still do germline testing in these cases?**

   No, the tumor has all germline variants. What you should check, though, is that the genes are fully covered at sufficient read depth in order to exclude a false negative call.

7. **Fantastic overview of molecular testing over the past couple of decades, Birgit! What are your thoughts on the current state of WGS/WES proactive testing of healthy individuals? Where do you think DTC WGS companies fit in, with respect to proactive testing?**

   Thank you! I am a huge fan of proactive testing and am finding current professional recommendations (ACMG) too restrictive and a bit paternalistic. I do understand that, as a society, the downstream cost to the health system does need to be taken into consideration, but in my opinion, it should not be discouraged to offer such testing. I am not enthusiastic about allowing this type of testing under the umbrella of DTC though. I have had enough visibility into this space, and cannot overstate the importance of qualified professional guidance, especially post-test. There are simply too many bad players that lack quality control and clinical scrutiny - paired with inadequate regulatory oversight, there can be too much damage.

   The International Consortium of Newborn Sequencing stated that they have a gene list committee that is helping to answer this question.

8. **An issue I've experienced lately is a certain distrust from the medical practitioners about contacting patients based solely on the genetic variants and info we've found. Do you think the situation will evolve with time or are there any tips you have regarding creating a "bridge" between both fields?**

   This is so true... I am very familiar with this problem and wish there were a quick fix. The only way in the short term is to invest in genetic counselors. Then the medical curriculum does need to catch up such that genomics is properly taught. Finally, this

is an area where I have high hopes for AI assistance… It is too early, but if there were easy to follow guidance embedded in the EMR that guides the provider, reluctance would hopefully lessen**.**

9. **Are any/most/many clinical labs going for long read now ab initio?**

   No, not yet. It is definitely on the rise but will likely take another five years at least to become mainstream. I see LR-NGS pop up in larger operations, and when an institution has the funding, it is an excellent addition as an adjunct technology (to fill gaps/weaknesses for short-range NGS, such as CNV/structural variant detection). I am expecting short read NGS to stick around like Sanger sequencing does, but it will eventually disappear. Short read NGS made its clinical debut in 2010, so 15 years ago. And we are still using Sanger sequencing for certain applications (e.g., confirmatory testing). I'd anticipate a similar timeline for the transition from SR-NGS to LR-NGS as a primary technology.

10. **With regard to symptomatic cases that reported negative for WGS. Current recommendations are either to wait a year for data reanalysis or, when new symptoms occur, should we reflex to long read sequencing WGS or consider RNA sequencing?**
    With the frequent variant reclassification, especially for carrier screening that only reports pathogenic/likely pathogenic, it is challenging to recall patients into the clinic. What is the acceptable timeline for follow-up in your experience?

    That is an excellent question. Ideally, this would be a continuous process that is executed in the background and alerts the lab when new publications are available that impact variant classification. After all, critical evidence can emerge, they say, after a result has been reported. That is not yet reality, but I am hoping that we will get there in a few years. Waiting a year is a pragmatic recommendation but is merely a blow to the fact that reanalysis is expensive and infeasible "whole scale". No lab (I know) is able to execute re-analysis for every case on a yearly basis.

    Reflexing negative cases to long read WGS would be one way to address false negatives that are due to deficiencies of short range NGS in calling all variants (most pronounced are its difficulties with CNVs and complex SVs). But that is quite expensive and infeasible for most labs!

    I am afraid that at this point in time, we (as a community) can only do so much and will likely continue to be reactive rather than proactive (i.e., re-analyze upon provider request, or when new knowledge becomes available in the context of a different case, prompting reanalysis of past cases).

11. **Thank you very much for the excellent lecture. My name is Safaa from Sudan, and I am a PhD student in Genetics and Molecular Biology. I completed both my bachelor's and master's degrees in the same field. I have purplish two scientific papers. Unfortunately, practical application opportunities are very limited here in Sudan. During the lecture, you mentioned training programs; would it be possible for me to obtain a scholarship to attend such training sessions?**

    Thank you so much for your interest in this field! Yes, there are training programs that are open to accepting international fellows, but there are a few limitations. Here is a resource where you can look up US-based laboratory genetics and genomics training programs (LGG). I assume that there are similar programs in Europe. https://www.abmgg.org/training-programs.

    US programs often have funded fellowship positions. However, most will not accept students who don't hold appropriate visas. The best visa to hold was an H1B visa, and some institutions were willing to sponsor this. But right now, this is likely no longer possible. I would encourage you to email the program directors (above link) and inquire about their current policies around this! And please check our European Training Programs, as those may have fewer limitations.

12. **How does a clinician decide whether whole genome sequencing or next generation sequencing, or whole exome sequencing which one is better for their patients?**

    Great question! It's not really a question of the "assay". Labs can use WGS (or WES) but offer a small gene panel. WES/WGS is often used synonymously with "analysis and interpretation of the whole genome for rare/undiagnosed disease" (often done by using patient/parent trios. And WGS and WES are really the same; WES is more common still simply because WGS is still a bit more expensive. If your patient has a well-defined clinical diagnosis where there is a high likelihood that a gene panel will yield a result, it is still considered best practice to order a gene panel (though the assay in the background can be WGS). An example is cardiomyopathies, where the diagnostic detection rate is often 40-60%. That said, if I were a clinician, I'd gravitate to laboratories that do use WGS (or WES) as the assay, as in that case, even if you start with a gene panel only, it is easy to reflex to a full-scale whole genome analysis if the case is negative. I hope that makes sense! The key is understanding when your patient's disease is not clear (but looking genetic). Many providers access genetic counselors to help navigate this question, but unfortunately, many still do not have such resources.