USING ROBUST QUALITY CONTROL TO IMPROVE CANCER CARE

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Precision Cancer Care Requires Accurate and Reliable Detection of Genomic Variants. Navican Are Using Robust Quality Controls to Make This Possible.

In order for a genomic test to have clinical utility, the provider needs to ensure that the assay is highly accurate so that patients are not negatively impacted by incorrect results. One such test provider is Navican, who are looking to provide precision cancer care that is as reliable as possible. To do so, they are collaborating with SeraCare Life Sciences, a leading provider of clinical genomics QC tools and platforms, to establish robust quality control systems that can identify errors in their workflow and detect problems before they affect patients.

Q: What is Navican's mission?

KG: Simply put, we're an end-to-end precision cancer care company. We don't view ourselves as just a testing provider. We want to bring the realization of precision medicine to patients, and that doesn't just include a genomics test. It includes giving patients access to a molecular tumor board of experts in the field, especially for patients and their oncologists in the community setting. Then the follow through is thinking about how we can provide these patients with targeted therapies, and that's when our navigation services kick in. They work with the oncologists, the patient, and the health plan to help with either giving them access to a targeted therapy or enrolling the patient in a clinical trial. It's there that we feel there's a missing link in the precision cancer care story for a lot of testing laboratories today.

Q: What is the importance of a robust QC program, and what are the challenges faced when building a best-in-class protocol?

KG: When you consider next-generation sequencing (NGS), it's a highly complex test. As you add analytes that consider DNA and RNA from FFPE specimens, especially for solid tumors, you're adding another layer of complexity to the testing. There are a variety of factors that can impact the quality of testing, from preanalytical considerations of the specimen to handling and processing, be it on the wet bench side, the biochemistry, the instrumentation, or the technicians involved in library preparation. After sample preparation, you still need to think about the steps involved in NGS and bioinformatics. There are so many sources of potential errors or noise in the system and they can all impact patient results.

BK: The idea is to be as robust and comprehensive as possible when gathering that data. It's what allows us to be confident in the results that we're reporting to our patients. Despite the complexity of these tests, we're able to capture any variance that could impact result quality and therefore patient care.

Q: How did biosynthetic NGS reference materials allow you to bring your assay to market sooner and with greater confidence in the diagnostic results?

KG: One of the big challenges you face when adding different variant types to your test is that it can be very difficult to get a large validation cohort of known positive samples. For example, a lot of fusion-positive samples are lung biopsies, and after diagnostic testing, there isn't a lot of patient material left over for analytical validation.

BK: There are a number of clinically relevant mutations that are relatively rare and hard to come by in clinical samples, but which are critical for us to be able to detect in patients who have them. That's one of the things that makes biosynthetic variants really valuable. We can check on those harder-to-find mutations or variant types to make sure that we can identify them appropriately, especially in the absence of a large clinical cohort.

KG: The other aspect of biosynthetic references is that they also add sensitivity to the tests and improve our ability to determine the lower limit of detection. They have been orthogonally validated for their allele frequencies, which allows us to have a high degree of confidence in detecting a lot of these challenging mutations at lower allele frequencies.

Q: Clinical genomics labs are making ever more impressive sensitivity and specificity claims; how did you establish your performance metrics and how have you been able to demonstrate them over time?

KG: One of the main challenges of bringing on these types of tests is the overall complexity. Initially, we turned to guidelines published by the College of American Pathologists and the Association for Molecular Pathology and used them as our roadmap for validating assays. With that guide, we designed what we believe is a very robust validation, consisting of a large patient cohort as well as cell lines, previously characterized FFPE patient samples, and biosynthetic standards. This enables us to be comprehensive in the way we assess assay performance, and we leave no stone unturned when it comes to the depth and breadth of variant and sample types, allele

frequency, sample quality, or relative variant fractions in the samples. You can only really account for the complexity by being as comprehensive as possible for validation and development of the assay.

Our sample diversity enabled us to determine the performance characteristics of our test. We then wanted to ensure that once we went into production, we were consistently meeting the performance we observed during validation. So we decided early on in our production that we would like to run a biosynthetic control, such as the SeraCare DNA and RNA standards, on every single batch or run in our clinical production. This was a strategic financial investment for Navican, because it costs money both for purchasing the biosynthetic standards and within our sequencing, but we believe it is very important for ensuring the quality of our testing. It really goes to our corporate mission of putting the patient first.

By running these standards, we can track the performance of every batch so that we can use the data to identify performance and quality trends. The controls contain a wide variety of variants that are at or near our limit of detection, so if we start to see performance changes that cause hard-to-detect alleles to dropout, we can detect it early on and make adjustments to correct the problem. This tracking covers everything from our wet bench processes, to our bioinformatics and variant calling processes and ensures that they are working.

What this assures us is that for every patient sample, we have a mass biosynthetic positive that we know has reached the quality standards we have set. So we can be confident that every test we sign out reaches the bar of quality we desire in assay validation.

Q: What software solutions did you use to build your QC protocol, particularly with rapid growth and scaling in mind?

KG: We've partnered with a number of industry leaders. One of these is Philips IntelliSpace® Genomics, who have built a clinical-grade platform that enables us to transition from ordering bioinformatics to variant review, interpretation, and sign out. We've then supplemented that with SeraCare and their iQ™ NGS QC Management platform to help us track the QC measures that are specific to the biosynthetic standards. Using these, we can generate reports and track assay performance — clinical samples with Philips and run controls with SeraCare.

BK: Our software also allows us to connect those platforms together, as well as to our LIM system, to build a comprehensive network that captures all the information we need to ensure quality in a way that is trackable.

Q: How did your approach to QC change as you moved into the post-launch, daily run control phase?

BK: One of the things that we do before generating any results is to set forth performance characteristics determined during the validation. These characteristics are reviewed every sequencing run, control sample, and patient sample, so that we know we are meeting our performance specifications before the variant analysis and reporting pipeline. As part of our overall QC program, SeraCare controls play a big role in making sure that our quality metrics and our data are meeting those specifications.

By observing the QC metrics of SeraCare standards and then the metrics of the patient sample, we can assign a quality to each run. This approach also lets us separate some of the different components of error that can be observed in an NGS assay. For example, if a sample falls outside of the bounds we expect when the biosynthetic control was within the threshold, it is likely that the problem is not a result of the sequencing. Instead, it's more likely to be an issue with that particular sample. It changes the way we troubleshoot the assay.

Q: What advice would you give to someone who is preparing to deploy their own clinical genomics assay?

KG: It really requires a massive upfront investment, to bring in the right people and talent, and then pairing them with the right processes and software. You can't underestimate all of the complexities and subtleties involved in this type of testing. There are a lot of factors that can impact test performance, so you really need a very robust QC program to make sure you're meeting that benchmark.

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