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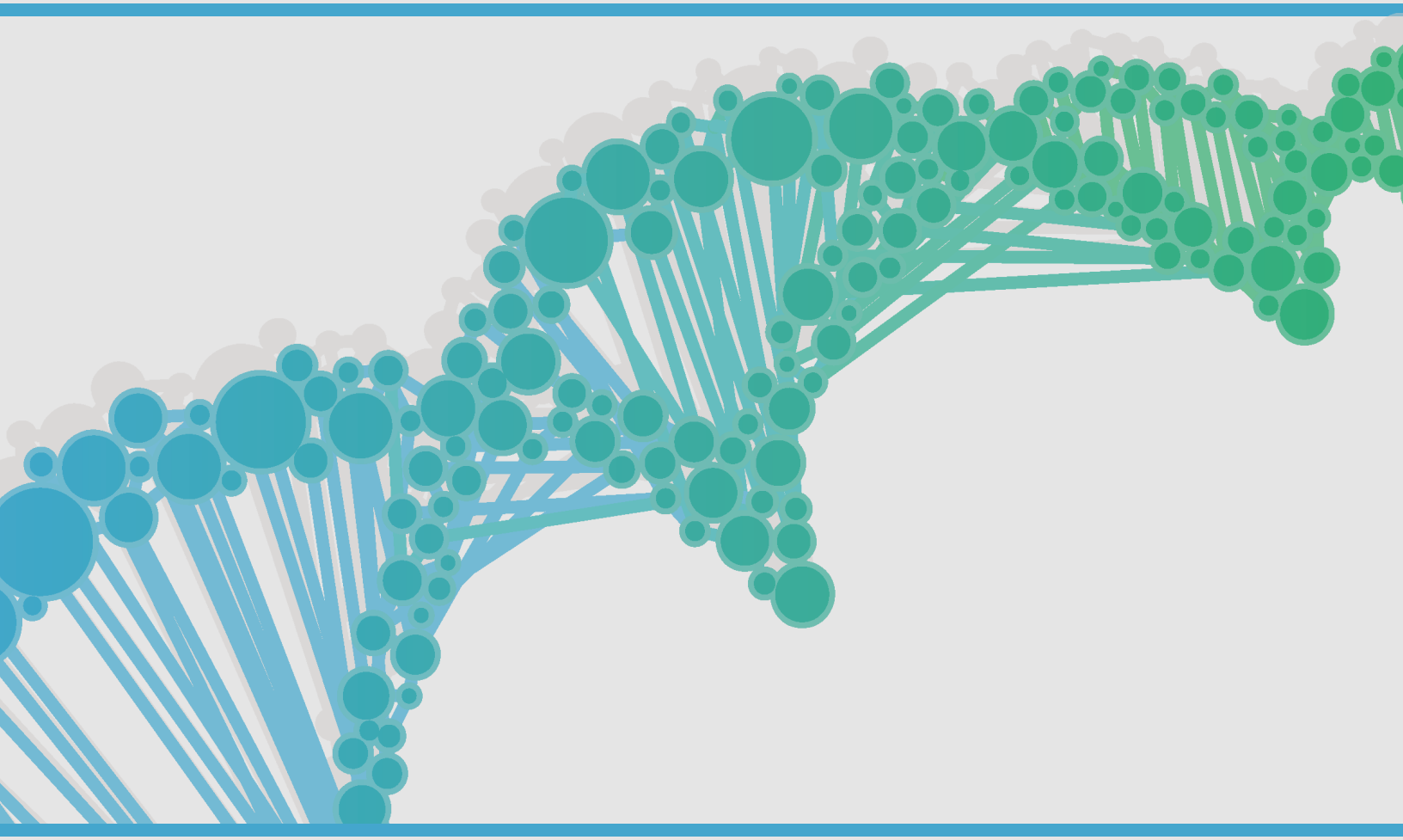

CLINICAL CONVERSATION

Optimizing and consolidating multiple testing strategies to increase efficiency with increasing testing demand

Dr. Ingrid Simonic, Deputy Director, Medical Genetics Laboratories, Cambridge University Hospitals,UK, speaks about the current state of testing strategies and future outlook.

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We spoke with Dr. Ingrid Simonic, Deputy Director, Medical Genetics Laboratories, Cambridge University Hospitals, UK, about the current state of testing strategies and future outlook.

Tell us a little bit about your testing lab.
We are a regional testing service serving 2.5 million people. Tests are requested by neonatologists, neurologists, community pediatricians, and clinical geneticists. About 15,000 tests are performed each year and one-third are for intellectual disability. It makes you wonder why there are so many tests. It's not because there are so many patients but we are doing loads of tests per patient. That is a lot of testing and perhaps we can do a little better by tailoring and consolidating rather than performing several tests per patient.

Dr. Ingrid Simonic, Deputy Director, Medical Genetics Laboratories, Cambridge University Hospitals, UK

What is your current testing strategy?
Our current testing strategy includes FISH, FRAXA, array CGH and SNP array as the first line of tests. Targeted MLPA and Sanger sequencing are used as the second line. TruSight One sequencing and targeted gene panel analysis is performed for sequence variant analysis as decided by clinical cytogeneticists. If nothing is found here, the patient is referred to the 100,000 Genomes Project where whole genome sequencing is performed.

What challenges do you see in your testing process and what can you do to overcome them?
We are facing increasing demand for NGS testing, particularly whole exome sequencing which is labor intensive and costly. We use an in-house sequencing pipeline for our panels and with large panels, the pathogenicity assessment process can be quite tedious. Streamlining the system would

benefit both the testing service as well as the patient by decreasing our costs and providing faster turnaround for the patient. One way to achieve this would be to consolidate the existing 2-3 stage consecutive testing workflow for constitutional referrals and replace it with a single SNV/CNV analysis pipeline. The first step in this process would be to see if CNV detection from the TruSight One panels is comparable with array CGH and SNP array results.

What made you use BioDiscovery's NxClinical to address this challenge?
In June 2017, we looked at SNVs in BioDiscovery's NxClinical for SNV selection and compared our local bioinformatics pipeline to that from NxClinical. The concordance was 100%; I was really impressed! So, when BioDiscovery approached me to try the new CN from NGS calling feature in the new upcoming NxClinical 4.0., it didn't require much persuasion to convince me. But, I was skeptical because the TruSight One only covers 12MB of the genome - the coverage is pretty patchy. So, I couldn't imagine how many of the CNVs we currently report would be detected with this patchy coverage.

"We looked at SNVs in BioDiscovery's NxClinical for SNV selection and compared that to our local bioinformatics pipeline. The concordance was 100%; I was really impressed!"

So, how did you go about with the analysis?
We used 137 TruSight One NGS samples for most of which we had available array data from Affymetrix CytoScan 750K arrays and for a portion of these we had MLPA results. Then we compared the results we got from NxClinical with the MSR algorithm that derives copy number from sequencing data to the results from arrays and MLPA tests.

What was the analysis and interpretation process like?
I realized later that for the validation, over 3000 chromosomal plots had to be reviewed! But I found it surprisingly quick to go through all chromosomes in all samples in NxClinical. A feature that I really, really liked is the ability to immediately see prior cases with similar events in the same view as the case under study. It is a marvelous feature; you click on an event and you can easily see how many times in the past this event has been seen in your database. It's really quick. But what took me really long is to go through our laboratory databases to review array and NGS files. These data are stored in three in-house databases which are essentially Excel spreadsheets. These spreadsheets work quite well but with large panels, the process is quite tedious.

So, the moment of truth…how did the results compare?
Results via the MSR algorithm in NxClinical were compared to prior array and MLPA analysis on the same samples. I found CNV calling from NGS in NxClinical accurate with 90% concordance between TruSight One and Affymetrix CytoScan 750K arrays. These results were great especially considering that we didn't have control samples from the same batch as these samples were gathered over two years. The control samples we used were from a recent batch but ideally one would use controls from the same batch.

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This sample was referred for Gitelman Syndrome testing. A small heterozygous deletion event affecting exons 1-7 of the SLC12A3 gene was detected in the proband using BioDiscovery's BAM MSR algorithm. Another homozygous deletion of the same region was identified in another sample in our series.The NGS data of the proband also identified a heterozygous pathogenic SNV variant: c.2965G>A p.(Gly989Arg) on the same gene. All these events in our series of patients could be detected in a single view using NxClinical.

"The ability to look at both AOH and sequence variants in the AOH regions is important as some of the populations in the area serviced are consanguineous."

Aside from those you already mentioned, is there another feature in NxClinical that stood out for you?

There is a really nice function in NxClinical which allows for looking at compound events. The ability to look at both AOH and sequence variants in the AOH regions is important as some of the populations in the area serviced are consanguineous. I was able to identify a homozygous stop gain in a gene which could be the reason for the referral but this gene was not in the panel we tested so that was really nice to find. The feature allows us to identify compound heterozygous events by displaying only SNVs in regions of homozygosity.

Final thoughts on your validation and in general on the testing field?

With rapidly advancing genomic technologies, for a large proportion of clinical referrals, we need to replace multiple testing strategies by NGS technologies. NxClinical allows for combined analysis of DNA copy number changes or regions of homozygosity with single nucleotide polymorphism analysis, incorporating all variants in one view and consolidating multiple tests to a single test. This provides numerous benefits such as identification of compound heterozygous events as well as rapid results provision which is essential for improved patient care. Now that I've started using NxClinical, I just can't go back to analyzing all these variants separately the way I used to.

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