New York Genome Center Developing WGS Tests for Women's Health

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BALTIMORE – With the goal to make whole-genome sequencing (WGS) routine clinical practice for women's health, New York Genome Center is partnering with Columbia University Irving Medical Center's Ob/Gyn department to develop women-focused WGS tests through their recently established Women's Genetic Center.

As part of the initiative, NYGC is testing out the new sequencing platform from Ultima Genomics in an effort to reduce sequencing costs. However, the nascent collaboration still has a long way to go to validate the new instrument and establish WGS tests for clinical approval.

According to NYGC CEO and Scientific Director Tom Maniatis, the Women’s Genetic Center was conceived about a year ago, after a "serious discussion" between NYGC and Columbia’s Ob/Gyn department to jointly innovate, develop, and implement clinical genomic tests for women’s health.

"Whole-genome sequencing is at the core of this initiative," said Maniatis, adding that the partnership is built upon the momentum of NYGC's earlier collaboration with Weill Cornell, New York-Presbyterian Hospital, and Illumina to test drive the feasibility of routine WGS in the clinic.

Currently, a revolving door of targeted molecular tests — such as karyotyping, fluorescence in situ hybridization (FISH), chromosomal array analysis, and carrier screening — are routinely clinically used in the Ob/Gyn field, Maniatis said. "Virtually all these tests, including cancer testing, can be replaced by whole-genome sequencing," he added.

Meanwhile, Maniatis acknowledged that "the big criticism" of WGS has always been its high cost, often making it not financially viable for routine clinical use. To solve the bottleneck, NYGC started eyeing a new sequencing platform from Ultima, a sequencing newcomer that promises to reduce sequencing costs to $100 per genome.

According to Soren Germer, who leads the sequencing and analytics teams at NYGC, the relationship between the center and Ultima was forged last summer, when the company was still in stealth mode.

Since then, the institute has been "kicking the tires" with the Ultima platform, having sent a handful of samples to Ultima for it to perform sequencing runs within the company and return results back for evaluation, Germer said.

After an initial evaluation by comparing the sequencing data from Ultima and Illumina, Maniatis said NYGC was convinced to purchase one instrument, which has just been delivered and installed at the center.
Now, Maniatis said the goal for NYGC is to apply the center’s "enormous experience" with Illumina whole-genome sequencing to the new instrument and further understand how the Ultima platform compares to its Illumina counterpart.

According to him, NYGC’s clinical laboratory, which currently houses several Illumina NovaSeq sequencers, was the first lab approved by New York state to offer clinical WGS tests for cancer. The institution has also sequenced over 50,000 whole genomes on the Illumina platforms throughout the past several years.

With that in mind, Germer noted that another attraction for the Ultima platform is its promised high throughput. "For the Women’s Genetic Center, we’re really focusing on genome sequencing at scale," he said, adding that he considers Ultima "the only Illumina game-changer right now."

Still, Germer said a lot of validation work is still needed to vet the performance of the Ultima system. To that end, he said the center will be running benchmarking studies with "quite a lot of samples" in-house, including both research samples and clinical samples that were previously used to validate NYGC’s clinical lab with New York state.

In addition, he said the NYGC is already conducting prenatal sequencing with Columbia’s Ob/Gyn department on the Illumina platform, and these samples, for which the center has obtained research consent, will also be sequenced on the Ultima instrument for a head-to-head comparison.

Although Ultima’s workflow largely resembles Illumina’s, Germer anticipates there will be some modifications in the wet lab tailored for Ultima. Similarly, he said the downstream data analysis pipeline will also be slightly different. However, he said once the data have been through variant calling, they will be “fairly straightforwardly” passed on to NYGC’s standard clinical interpretation pipeline, generating end results in the same formats as the Illumina sequencing data.

One technical limitation for Ultima sequencing is that the platform currently cannot call homopolymers longer than 11 bases, Germer noted. While he said he still needs to see what effect that has in terms of clinical variant calling, he is confident that as the technology continues to improve, it will work "in a reasonable manner." He also said that NYGC is hoping to collaborate with other institutions that are also Ultima’s early-access customers to improve the quality of the platform’s variant calling.

As for some researchers’ reservations on Ultima’s use of off-instrument emulsion PCR to generate amplified DNA for sequencing, Germer, who used to be involved in 454 sequencing, agreed that emulsion PCR was “really a pain” back in the day. However, he thinks that with Ultima’s automation, emulsion PCR is largely a "historical headache" and is not really something he is "terribly worried about."

Despite the promises that Ultima sequencing may bring, Maniatis said that the Women’s Genetic Center will not be confined to a single instrument. "We’re going to use the best technology that’s the most affordable, and this is an opportunity for us to really compare them," he said. Similarly, Germer said if Illumina comes out with a very competitive product the center will definitely consider it.

Maniatis said the Women’s Genetic Center is currently supported by the existing infrastructure from both NYGC and Columbia Ob/Gyn. However, he said the initiative is also currently posting jobs for its director, business staff, and other positions. Once fully established, the clinical test offerings of the Women’s Genetic Center will also be absorbed within NYGC’s overall clinical program umbrella, he added.

In the long run, Maniatis said the goal for the Women’s Genetic Center is to establish and offer WGS-based clinical assays that can replace the plethora of targeted tests currently used in women’s health.
Once developed and proven to be effective, he said the assays will be first catered to Columbia's Ob/Gyn department. Meanwhile, depending on the outcome and success of the assays, Maniatis said NYGC is also open to additional collaborations with other hospitals perhaps in New York City and beyond.

However, with insurance approval anticipated to be one of the major hurdles, Maniatis said the center needs to not only reduce the cost for whole-genome tests but also demonstrate the value of WGS, as it can eliminate the need for multiple tests while providing far more biological insights than the current standard of care.

In addition to test development, the Women’s Genetic Center also has a research component to continue exploring the applications of the latest genomic technology — such as long-read sequencing, liquid biopsy, single-cell technologies, and optical genome mapping — toward women's health, Maniatis said.

In that effort, he said that NYGC will utilize the samples made available through the collaboration with Columbia. "One of the most difficult things about advancing genomics and research is having access to patient samples," he said, adding that the samples made available to NYGC through the partnership will be "mutually beneficial" to propel research for both entities.

"The idea would be any profits that would come out of the tests would be driven into research to continue to explore new genomic methods in women's health," he said.