

Scalability, flexibility, and collaboration: how a small lab can compete like a large one

In November 2015, the Swiss prenatal diagnostic laboratory Genetica became the first company in Europe to run the Natera Constellation platform. Using Constellation, Genetica is able to offer Panorama testing locally, developing and validating clinical assays at their own facility.

Genetica began offering noninvasive prenatal testing (NIPT) in 2013, and the test they chose to use was Natera Panorama—a market leader. To perform the test, Genetica would accept the samples onsite, then send them to Natera's laboratory in San Carlos, California, for processing and analysis. But circumstances, including increased demand and changing regulations, necessitated a move from offsite testing to onsite testing. Genetica made the decision to license Natera's Panorama test and run it onsite, using Natera's Constellation software platform for data analysis.

Prior to this project, Natera had never licensed Panorama to another laboratory. Further, Constellation had not yet been launched in Europe, so licensing to a Swiss company entailed working through a new set of regulations. In the meantime, Genetica, a small laboratory with finite resources, had to trust that their decision to transition to Constellation was the correct one: a costly mistake would have been catastrophic to their company. Additionally, because Genetica is a small laboratory, both companies needed to ensure that Constellation's scalable platform and Panorama's workflow would scale down to effectively serve Genetica's needs.

Genetica and Natera's Panorama test

Genetica was founded in 1985 in Zurich, Switzerland. They are a single lab facility that employs sixteen people and specializes in genetic diagnosis, with a strong focus



in prenatal diagnosis. They serve approximately 4% of all Swiss pregnancies. When Genetica made the move to NIPT in 2013, they chose to offer the Panorama test by Natera.

Despite being the last NIPT test to market (2013), Panorama quickly became the market leader. With more than 600,000 tests performed, it is one of the most widely used NIPTs available. Panorama is able to provide accurate readings, even with very low fetal fractions (2.8%), which means that patients can get the answers they need as early as nine weeks into pregnancy.

For Genetica, an exhaustive evaluation of the scientific literature concluded that Natera's single-nucleotide polymorphism (SNP) technology offered technical advantages that other NIPT technologies could not. For one thing, SNP technology was the only one that could clearly differentiate between maternal and fetal cfDNA. Further, Natera had solutions that met EU regulatory requirements, in the form of CE-marked reagents and CE-marked bioinformatics.

Constellation partner labs are provided with proprietary reagents and protocols that are based on best practices, as employed by Natera's own CLIA-certified lab in San Carlos, California.

To offer Panorama testing, Genetica accepted the samples onsite, then sent them to Natera's laboratory in San Carlos, California, where they were processed and analyzed. Results were returned to Genetica within approximately two weeks. But when, over the next couple years, demand for testing grew and regulations changed, Genetica had to reassess how they offered NIPT.

The decision to move to Constellation

It was announced that, in July 2015, Switzerland's statutory health insurance (obligatorische Krankenpflegeversicherung, or "OKP") would begin reimbursing NIPT. But there was a catch: all steps of the NIPT analysis would have to be performed domestically

in Switzerland. To be eligible to receive reimbursement, Genetica would either have to develop its own NIPT or license an existing test.

For Genetica, licensing an NIPT was the better choice. Developing a new NIPT is not only expensive (research and development require millions of dollars), but it can take years. There is also significant risk that a new test might not be validated or meet regulations. Furthermore, through Panorama testing, Natera and Genetica already had a working relationship.

To provide Panorama quality from their own facility, Genetica made the decision to license the test directly and to perform the requisite data analysis using Constellation, Natera's turnkey scalable bioinformatics application. With Constellation, raw NGS data could feed directly into the software platform, where the Natera bioinformatics algorithms processed the data and returned sample results. No personal private medical information is ever passed to Constellation, and all data is encrypted during transport. Further, because analysis is handled on a server, there is no need to procure expensive high-performance computer hardware or—after the initial reconfiguration (if needed) of a laboratory information management system (LIMS) and the installation of an application programming interface (API)—to maintain a team of IT techs for the bioinformatics.

Constellation partner labs are provided with proprietary reagents and protocols that are based on best practices, as employed by Natera's own CLIA-certified lab in San Carlos, California. They also receive complimentary technical support. During the initial implementation of Constellation, Natera provides a team of applications scientists to work with the partner lab in tailoring protocols and workflows.

The technology transfer process

Once contracts were signed, Natera's applications support team worked right away to provide Genetica with protocols for setting up in-house testing.

Equipment (machines and tech)

Genetica had been doing next-generation sequencing (NGS) for about a year prior to the Constellation implementation, so their laboratory was already partially equipped to perform Panorama testing. (Aside from the sequencing machine, tools used in the process are primarily standard laboratory equipment.) Genetica's equipment purchases included an Illumina HiSeq 2500, a Hamilton Genomic STARlet, a Hamilton Microlab NIMBUS, one laminar flow hood, three freezers, a refrigerator, four PCR cyclers, and two computers.

When processing a Panorama test, a laboratory information management system (LIMS) is necessary for tracking and attaching patient metadata to the samples. The LIMS communicates with Constellation by passing data through an application programming interface (API). Prior to this project, Genetica had maintained a homebrew LIMS that was not originally designed to “talk” with external applications like Constellation; because it was required to function with the Constellation API, the LIMS had to be redesigned. Genetica does not employ bioinformaticians, so they outsourced the API installation; after the installation, they adapted their LIMS accordingly.

Workflow

Genetica started with the standard Panorama NIPT workflow and protocols that Natera provided, then conformed them to suit their specific environment. For example, Natera protocols required an additional room to minimize cross-contamination, and Genetica was able to work with the specifications to construct a room that required less space than initially anticipated. The Natera protocols also had flexibility for automation, so Genetica automated the majority of their workflow. Not only did their automation improve quality by avoiding inconsistency and sample swap, but because Swiss labor is very expensive, it led to noticeable cost savings.

Genetica’s workflow starts every two to three days—when there are enough samples collected to fully load the DNA sequencer. NIPT at Genetica requires one manager (for troubleshooting and fine-tuning) and three to four part-time technicians, at least two of whom are dedicated each day to Panorama testing. With automation and the appropriate personnel for the workflow, Genetica has been able to process approximately 220 samples per month.

Issues that arose during the adaptation process were discussed during weekly phone calls. Genetica kept Natera informed of all adjustments, and Natera provided answers and guidance as needed. Ultimately, Genetica was able to align Natera protocols with the workflow they crafted for their specific laboratory, demonstrating



the flexibility and scalability of Constellation in a real-world environment. Genetica effectively conformed Constellation to fit the needs of their lab.

Training

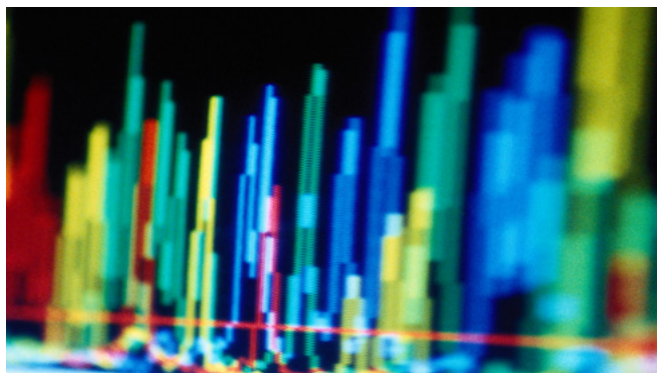
During the implementation, Natera engaged in weekly calls with Genetica. Natera’s team remained flexible in conducting these calls, accommodating a significant difference in time zones.

Because Genetica had worked with NGS and Panorama for at least a year before project implementation, Natera was able to forgo some of the Constellation training procedure (e.g., sample collection, preparing the DNA library, sequencing), skipping ahead to instructing Genetica on the finer points of analysis and interpretation of the bioinformatics. One Genetica representative said that the team found training on interpretation of the results garnered using the new methods to be easier on account of the prior experience with Panorama.

Prior to the technology transfer, Natera provided Genetica with laboratory demonstrations of the Panorama process. Genetica technicians were invited to the CLIA-certified laboratory in San Carlos, California, to see how Natera experts conducted testing.

Flexibility and collaboration

Three issues made this particular case a complex one. First, prior to Genetica, Natera had never licensed Panorama to an outside laboratory. With Genetica providing a partner laboratory’s point of view, the two companies collaboratively developed the licensing procedures that are currently in use for Constellation implementations.





Second, this project marked Constellation's launch in Europe. Natera needed to ensure that Panorama and Constellation complied with international regulations.

Third, Genetica's laboratory is significantly smaller than Natera's, which required that both the Panorama workflow and the Constellation platform be scaled down. Working with smaller sample amounts required different strategies. Smaller samples also resulted in some laboratory issues, which Natera and Genetica were able to collaboratively troubleshoot. For example, while Natera ran gDNA and cfDNA separately, it was not cost-effective for the volumes handled in a smaller lab.

The Panorama test reads samples at different depths. The standard workflow involves pooling samples to undergo high depths of read (HDOR) separately from samples that will undergo low depths of read (LDOR). Running HDOR and LDOR sample pools separately was not feasible for Genetica. To create an effective and reproducible method of pooling different types of samples on a single sampling run, Natera and Genetica created a calculation method that suited Genetica's specific needs. As a result of this project, calculator creation is now a standard part of Natera's training for new partner labs.

Verification and validation

The verification and validation (V&V) process is an important step in any clinical test. During V&V, a team gains experience with the product and confidence in the quality of the analysis; possible issues with the workflow are discovered and rectified. Natera's applications team made the V&V process seamless, supplying protocols and positive controls for the V&V steps as well as walking Genetica through the entire V&V process. In the first phase, the lab had to evaluate the analytical results for each of the crucial steps of the workflow. Natera provided samples for the lab to perform their testing on, then allowed the results to be compared to matched controls. The lab also had to verify the operability of the API protocols to ensure proper upload and data analysis between Genetica's system and Constellation. Genetica executed the entire protocol using Genetica-obtained samples, validating the protocol end-to-end. Here, Natera provided both negative and positive controls.

Conclusions

In this case, Natera's Constellation platform with Panorama in-licensing proved to be flexible, scalable, and adaptable. Despite the increased complexity of this implementation, Constellation was effectively installed to conform to the needs of a smaller lab while aligning with a new set of national regulations. In the meantime, Panorama continued to show itself as a stable NIPT requiring minimal laboratory space and few laboratory personnel. The customer, Genetica, was able to craft a workflow that aligned their lab's needs with Natera guidelines and Panorama standards. They were even able to create and incorporate additional automations.

In addition to the products themselves, Natera included a team of professionals to support the implementation process. Natera and Genetica worked diligently and collaboratively to ensure that any issues that arose were successfully resolved and that the implementation process remained on-track. Several of these collaborative efforts, including the pooling calculator, are now standard parts of the Constellation implementation process. The Natera team stayed readily accessible to the customer, despite the distance and the difference in time zones, and was able to provide guidance throughout the project, as well as efficient and timely validation and verification.

Overall, the Constellation software platform proved to be the scalable, adaptable solution that Genetica required. Using Constellation in conjunction with the Panorama test, Genetica successfully provides their patients with timely, onsite state-of-the-art NIPT testing.