Building a state-of-the-art clinical research sequencing lab in Israel

Genomics center established in record time to combat COVID-19 pandemic

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The novel coronavirus disease (COVID-19) pandemic has spurred biomedical innovation and motivated scientific collaboration. For Shamir Medical Center in Israel, COVID-19 was the catalyst to establish an onsite genomics center. Primarily focused on sequencing coronavirus variants, this next-generation sequencing (NGS) lab is developing innovative protocols for comprehensive genomic profiling and other clinical research applications.

Nir Rainy, PhD, who leads the new Shamir Genome Center, has spent his career on the forefront of technology. With his expertise in biomedical automation and with support from Illumina and Danyel Biotech,* Dr. Rainy set up a fully operational genomics lab in only three weeks. Shamir Genome Center is now the primary COVID-19 testing site in Israel, sequencing more than 1600 samples per week. We spoke with Dr. Rainy about what it takes to build a high-throughput genomics center, how his lab is aiding COVID-19 surveillance efforts in Israel, and his vision for the future of NGS in clinical research.

Q: What is the mission of Shamir Medical Center?

Nir Rainy (NR): Shamir Medical Center is the fourth largest public hospital in Israel. We serve over one million patients and provide personalized care to our patients in various specialty and sub-specialty fields. In addition, Shamir Medical Center is a hub for cutting-edge research and we strive to provide the best technology and care for our patients.

* Danyel Biotech is the Illumina channel partner in Israel. As an authorized distribution partner, Danyel Biotech gives customers access to Illumina products while providing the same level of sales, marketing, service, and support offered directly by Illumina.

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Q: Why was it important to establish a genomics lab at your hospital?

NR: Over the past few years, the hospital discussed options to establish an in-house NGS unit for pathology needs, as well as genetics, molecular diagnostics, and research at the hospital. The final push and catalyst to move forward was the COVID-19 pandemic. Shamir Medical Center was chosen to take part in the national sequencing efforts starting in 2021. By sequencing high volumes, Shamir Medical Center was able to build its own sequencing center and run the NextSeq™ 550 Systems at high capacity, lowering the cost of sequencing. We adopted a bottom-to-top approach in which we efficiently managed procurement, reagents, manpower—and overnight operations at times—to fully utilize the hospital network topology. Our main customer for COVID-19 sequencing was the Ministry of Health of the state of Israel. Since the establishment of the Shamir Genome Center, we have gained additional customers from pathology, genetics, microbiome, and other departments, as well as external customers.

Q: What attracted you to joining the Shamir Genome Center?

NR: I am a technology early adopter and I spent most of my professional career integrating biological questions and innovative technology. I prefer looking at several scientific questions, for instance in immunology, molecular biology, and genetics, and then applying state-of-the-art technologies to resolve some of those questions. I am attracted to the breadth of biological research done at Shamir Medical Center and believe cutting-edge multidisciplinary projects will require NGS and our dedicated services.

Q: How did your background prepare you for this role?

NR: I hold a PhD in molecular immunology as well as extensive training as a programmer and systems analyst. In the beginning of my career I worked as an immuno-oncology scientist and I was responsible for screening ligand–receptor interactions. After developing several tools and expanding the activity to a larger scale, we implemented automation and I gained deep and thorough knowledge of the automation process. Then, as an application scientist for Beckman Coulter automation systems, I learned how to do full-scale, automated NGS, how to write scripts, how to validate and execute protocols. Currently at Shamir Medical Center, I very much enjoy applying my knowledge and passion for a wide range of biological questions. The experience I've gained helps Shamir Medical Center ensure the best results for patients and customers.

Q: Why did you choose Illumina sequencing systems for the Shamir Genome Center?

NR: We chose Illumina sequencing systems based on our extensive experience, the platform flexibility, quality of service, and our excellent relations with Illumina Israeli distributer, Danyel Biotech. Illumina brings a very flexible solution that allows us to sequence exomes or microbiomes—basically, you can do everything on the same machine. In order to work quickly and with high efficiency, even during a pandemic, it was important for us that the NGS platform be able to utilize a wide range of reagents for the library prep stage, and that's exactly what we got with Illumina sequencing systems.

In March 2021, we got the green light to purchase the first NextSeq 550 System and less than 3 weeks after that, our lab was fully operational, running the Illumina COVIDSeq™ Test (RUO) with 384 samples per run. To comply with our main customer's demands (the Israeli Ministry of Health), we spent days and nights in the lab until validation was completed successfully. Dedication of the hospital management, IT, and laboratory workers was essential to our success, as well as to rapid deployment.

Q: How did you implement a high-throughput NGS workflow so quickly?

NR: We were able to make this happen due to our vast professional experience and prior knowledge. A lot of experience and know-how, in short. Before we started our lab at Shamir Medical Center, I already had a predesigned plan for the workflow, including what equipment would be needed. A Qubit fluorimeter, a plate reader, and almost anything else that was needed to start the lab was loaned to us at the beginning. It's been difficult to get 384-well plates, PCR plates, robot tips, etc, due to the high global demand for plastic consumables. Very generous help from our collaborators and supporters in the Israeli biotech ecosystem enabled us to overcome these obstacles, and we thank them.

We got the first NextSeq 550 System from Illumina within a few weeks, followed by rapid delivery of a Hamilton NGS Star liquid-handling robot. It took us less than a week from unpacking the equipment to post validation. Everything was achieved very quickly because the entire management team in the hospital was absolutely dedicated, from procurement to IT to infrastructure management. Red tape issues were resolved almost immediately, which was unheard of at the time in a big public hospital in Israel.

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Q: How did Danyel Biotech support you as you were setting up your lab?

NR: We have excellent relations and support services from Danyel Biotech, the distributor in Israel for both Illumina and Hamilton. We appreciate their expertise and direct contact with the application specialists, both for automation and Hamilton. We feel we are really in good hands. During this very rapid, somewhat chaotic time of establishing the Shamir Genome Center, Danyel Biotech came in to help, advise, and support by phone or remote access to the NextSeq 550 System, even on weekends. One weekend, we had a probe that was broken in the robot gripper and someone just came and replaced it at noon on Friday before Shabbat started. It is really amazing to have the safety net and level of service from Danyel Biotech.

Q: How is Shamir Genome Center helping COVID-19 research and surveillance efforts in Israel?

NR: Our COVID lab is open 24/7. We have a relatively short turn-around time from sample receipt to bioinformatics analysis to final report. At the moment, we've implemented a seven- to eight-day SLA† for each run. Our bioinformatics pipelines enable us to determine COVID-19 variants in less than 24 hours, complete with a list of critical mutations and this later is integrated into a comprehensive demographic analysis. We then work another 24-48 hours on the final report. We strive to improve this time but not at the expense of quality control. We won't lessen the strict measures we take in our process to ensure the results are accurate and that our report is crystal clear to decision makers in the Ministry of Health, Israel. Due to our dedication and level of service, the Ministry of Health asked us to remain onboard and further develop our sequencing capabilities. We are currently the busiest NGS COVID-19 sequencing lab in Israel and since March 2021 we have sequenced more than 18,000 samples.

Q: How has your process impacted your results?

NR: The process has implications for failure rates and concise results. We only have around 7% failed libraries in each run, which is an excellent benchmark. Based on past experience and speaking with colleagues, a 9-11% failure rate is more typical. This success is

† SLA, service level agreement

mostly due to deep understanding of the limitations and potential of automation. For example, if you see a gradient, then you know that you need to mix better. If the beads do not settle quickly, then it means you need to extend step times. When you choose the right automation protocols, you can see better results. Additionally, we have bioinformatics expertise. We've gained knowledge that allows us to correctly assess samples even if their quality score is low. For example, if we get lower coverage of a region, but we see some mutations that we know, we can score it and declare a certain variant.

Q: How are you using your sequencing systems?

NR: We have two NextSeq 550 Systems and one MiSeq™ System. Our vision is to have a NovaSeq™ 6000 System by the end of the next year. The NextSeq 550 Systems are going to support COVID-19 for the next two years. In addition, they will support TruSight™ Oncology 500 assays and the small-scale exome sequencing we are planning to start later this year. With the MiSeq System, we are going to implement Archer panels, 16S, 18S, and also SOPHiA assays for hematology panels. The future NovaSeq 6000 System will be used for interesting research with unique genomes and high-throughput exomes.

Q: How have you used automation to improve your process?

NR: We use automation to maximize sample throughput and overall flexibility. The automation script for the Hamilton robot was developed by Danyel Biotech. Initially, it was designed for 384 samples per run and Eppendorf tubes for the source material. During the implementation we modified the script to support 96-well plates as the source. Mostly we are doing 384 samples, but we can do 24, 48, 72, or 96 samples and we have jumps of 96 samples after that. We have immense flexibility with automation and also flexibility to use the mid-output or high-output flow cell on the NextSeq 550 System. On rare cases that require a quick answer to identify a COVID-19 variant, we can do a manual library preparation and run 24 samples on the MiSeq System.

We are also finalizing the validation and evaluation of TruSight Oncology 500. In a few months, we will be the first certified NGS lab in Israel that will fully automate this assay. Currently in Israel it takes three to five weeks to get results for TruSight Oncology 500

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or for exome sequencing for rare diseases. We are aiming to cut that time in half and bring results to customers in two weeks. Hopefully, we will grow and be able to serve more customers with the best possible solution for them.

Q: How else are you innovating?

NR: Our success with COVID-19 sequencing has paved the way to new collaborations with big pharma companies, academic researchers, and defense organizations. Also, we dedicate 10% of our time for innovation—intriguing projects we want to do and then try to develop into a product or a service. Our versatile team are always seeking new ideas to stretch the boundaries of our capabilities. What can we do for the hospital? What can we do for researchers? In a sense, we are a small start-up company inside a big public hospital.

Q: What is your vision for Shamir Genome Center?

NR: Our vision: We are aiming to be the best genomic center in Israel, in a few years, serving tailor-made solutions for various customers. Innovation will allow us to be leaders in our field and expand in other areas.

Q: Where are you taking NGS next?

NR: Taking NGS to the next level will have to include miniaturizing tests and enhancing cost effectiveness. Being able to shorten the sequencing run time might help us shorten reporting time. Being able to combine different tests on the same run, for example, TruSight Oncology 500 and whole-exome panels together with 16S amplicons will be very beneficial. Today, this is not feasible unless you know how to calculate the molarity perfectly and have super precision in pipetting. But most people will have failures and will have some of the libraries overriding other libraries. We want to develop tools that will allow us to do many tests on the same run.

Learn more

NextSeq 550 System, illumina.com/systems/sequencing-platforms/nextseq.html

Illumina COVIDSeq Test (RUO), illumina.com/products/by-type/clinical-research-products/covidseq.html

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