Illumina software project lead Aneesh Natarajan in a lab at the San Diego headquarters. Photo by Kristy Walker

Inside the new Illumina MiSeq i100 Series: The making of the software

What's it like to build the software in a brand-new sequencer? Illumina's Aneesh Natarajan takes us on the journey

Illumina recently launched the MiSeq i100 and MiSeq i100 Plus Systems, two powerful, compact benchtop sequencers that incorporate more than 140 invention disclosures and 60 patent families. On our News Center, we are celebrating outstanding employees who helped develop this breakthrough technology.*

THE ILLUMINA MISEQ i100 Series, announced last fall, is the company's first customer-installable instrument since the iSeq. Illumina's latest offering was a brand-new challenge for Staff Software Technical Product Manager Aneesh Natarajan.

When Natarajan began work on the confidential project in September 2021, only a select handful of employees knew about it. His manager, Bret Langham, asked him to represent the entire software department and serve as the software project lead. "To be on the core team of a new instrument project is a really good opportunity, and I jumped on it," he says.

Inside Illumina

Illumina's software organization is responsible for a portfolio that includes cutting-edge AI algorithms like PrimateAI-3D and industry-leading software solutions such as DRAGEN, winner of the PrecisionFDA Truth Challenge V2.**

The software department itself is divided into three disciplines: developers, testers, and technical product managers. Natarajan is part of the third category and works on the software that users interface with when operating an instrument.

Growing up in the San Francisco Bay Area, Natarajan always liked math and science. He landed at the University of California, San Diego, for college—less than two miles from Illumina's global headquarters. He majored in bioengineering, not computer science, specializing in bioinformatics (a discipline used heavily in genomics, which produces a large volume of data). In his final year of college, Natarajan's teaching assistant mentioned that a friend working at Illumina was asking

** illumina.com/systems/sequencing-platforms/miseq-i100.html*
*** illumina.com/science/genomics-research/articles/dragen-wins-precisionfda-challenge-accuracy-gains.html*

him to recommend people for a job. He encouraged him to apply, and that friend at Illumina became Natarajan's current boss.

Now, as a staff software technical product manager, his daily responsibilities involve working with all kinds of teams with varying levels of technical expertise. A hardware engineer might ask him to build software that can run a calibration routine. A product management director might suggest that low-throughput customers could use a feature in their software to reanalyze their data. Every day holds a new opportunity to collaborate and solve problems.

Behind the MiSeq i100

For a project like the MiSeq i100, a hardware team begins building what they call the "prototype one," or P1, instruments and consumables. Natarajan's initial goal was to construct the bare-bones software that would allow the hardware teams to manufacture the P1 instruments and test them as they build. This first version is called the service software, and it's used not only in manufacturing but also when field service engineers are troubleshooting an instrument.

Very soon after the initial service software gets off the ground, the team splits into two groups—one continues to create manufacturing tests for the service software while a second group begins to work on the customer-facing application, called the control software. They start importing all the sequencing functionality and building in some of the features that users will need.

One of the major efforts for the MiSeq i100 was developing the first-time setup for the user, which needed to be as easy as possible for users. The software guides the user step by step so they can install it independently without an Illumina field service engineer. Building this detailed workflow was extra challenging: Illumina's last customer-installable instrument, the iSeq System, was built on Windows, and the user had access to the underlying operating system. Natarajan's team would be building the MiSeq i100 on Linux, which would require a far more sophisticated setup workflow since the user would not have access to the underlying operating systems to configure their instrument. Natarajan's team wanted to provide instead a simple and intuitive workflow within the software user interface itself that would allow a customer to apply all their necessary configurations.

Through analysis of many customer use cases and potential failure modes, they worked out what information they'd need and what screens they'd require to connect the instrument to a customer's network. "Companies sometimes have massive IT departments because they have very unique networking requirements," Natarajan explains. "Our instruments need to be able to connect to any type of network, no matter how complicated or simple." They had to prepare different workflows based on a wide range of potential network configurations.

Writing these steps and accounting for all the possibilities, during setup and beyond, requires deep collaboration across the business. "Imagine the software detects some sort of hardware failure," Natarajan says. "What error message should we show to the user in that scenario? We have to work with the subject matter expert of that piece of hardware, because they would know the corrective action and what we should recommend to the customer. And then with the technical writing and experience design (XD) teams, we figure out how to craft that message before we put it into the software."

An XD team within a larger user experience team makes high-fidelity mockups of how the software should look in terms of font sizes, button sizes, color schemes, and so on. When they have the detailed requirements, they deliver them to the UI developers and software testers so they know what screens to build, and how to test that the software does what the stakeholders intended it to do.

Beyond setup, calibration, and other maintenance considerations, there is—of course—the actual sequencing. MiSeq i100 can run up to 384 samples in a span of four to 16 hours, depending on run configuration. All of this requires a sleek and streamlined user interface. "The customers don't want to spend a lot of time setting up a run," Natarajan says. "They often want to be able to plan the details of their runs ahead of time, so when it comes time to start sequencing, the workflow is quick and simple. They subsequently want a streamlined way to get their secondary and tertiary analysis results. To support these needs, we have features across our run management software, our instrument software, our cloud software, and our bioinformatics pipelines that allow the user to plan their runs and analysis, stream data to our cloud platform, BaseSpace Sequence Hub, and auto-launch analysis either on instrument or in the cloud."

At this point, the software team is ready to bring in other software components. They start with Real-Time Analysis, which is needed for sequencing. They add Illumina Run Manager, which handles a lot of the run

planning, run management analysis, and execution. They start bringing DRAGEN on board, which will analyze the data. They begin doing the cloud integration. They compile all the features they need to build a full digital package and launch the product; then they begin testing the software, cleaning it up, and making it completely customer-ready.

Natarajan is most proud of the effort the team put into embracing and building what the company calls "universal software"—meaning that the MiSeq i100 and NovaSeq X leverage many of the same software components, even though the instruments are very different. Many Illumina systems launch in staggered years but are built in parallel. Universal software allows everyone to work more efficiently and benefit from previous upgrades, improvements, and new features. "If we build new features on top of what NovaSeq X has, then theoretically NovaSeq X can pull those features into their subsequent software releases," Natarajan says. Best of all, universal software gives the customer a more consistent experience across all instruments in the Illumina portfolio.

The final stretch

Late summer 2024 was crunch time. Natarajan flew to Singapore to work with some of his software colleagues (the last two or three years of MiSeq i100 software development occurred mostly in Singapore while much of NovaSeq X was being built in San Diego). It was time to get the product ready for customers. "We want to make sure the product is as bulletproof as possible," he says. "No one wants the user to make an error because the software workflow itself was not intuitive enough."

The Illumina MiSeq i100 Series was introduced to the market in October 2024. Natarajan says, "There are so many exciting features in MiSeq i100. And I'm thrilled when I hear users say the software is extremely easy to use." ◆