

Pacific Biosciences' New Sequel IIe System Puts Focus on High Read Accuracy

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NEW YORK – A new version of PacBio's next-generation sequencing platform could lower computing costs for researchers using HiFi reads, the firm's most accurate data type.

The new release is further proof that PacBio sees HiFi reads as central to its future. The data type offers accuracy approaching that of Illumina's short-read platform, with longer read lengths, according to the company.

"There's no reason to delay in shifting customers onto HiFi" reads, said Luke Hickey, senior director of strategic marketing at PacBio. "The future is definitely HiFi. Any future major product releases will be HiFi-centric."

With a combination of four times more onboard processing power for post-collection data analysis and software upgrades, the Sequel IIe can natively generate HiFi reads by having the instrument condense sequences into the data type. "HiFi read generation occurs in much less time than it takes to perform sequencing," said Justin Blethrow, PacBio senior product manager.

PacBio expects customers to see the main benefits on the computational side of sequencing, where the optimizations have eliminated the need for post-processing of sequence data and could reduce secondary analysis times by 70 percent, Hickey said. In addition, the instrument could reduce data storage costs for customers by as much as 90 percent because they need to sequence less for the same project. "There's less to store," he said. "Being very long and accurate, you need a lot less coverage, a lot less raw data."

"With smaller files coming off the instrument, it makes it possible for customers to skip investing in an high-performance computing cluster of their own," Hickey said.

The sequencing chemistry remains unchanged for now and the instrument will continue to use the existing SMRT cell flow cells. "Our R&D team is now back in the lab working hard and we will address our chemistry improvements at a future date," Blethrow said, noting that the instrument redesign left "headroom for future chemistry improvements." Sequencing run times and output will also be unchanged on the Sequel IIe.

"Any steps that improve the throughput of the platform and the independence of the platform are welcome changes," Shawn Levy, a researcher at the HudsonAlpha Institute for

Biotechnology who uses HiFi reads in his work on human genome sequencing, said in an email. "We will upgrade the instruments in my lab to the IIe version as soon as it is available. "

The new sequencer may not be as well received by core labs that already have their own computing infrastructure, though. "It probably won't benefit us because we have our own pipelines and servers," said Molly Zeller, a research specialist at the University of Wisconsin-Madison's Biotechnology Center DNA Sequencing Facility. But the focus on HiFi reads is no surprise, she added. "Our PacBio business is booming" largely due to HiFi sequencing, she said. "There's no going back now, it's HiFi or bust."

PacBio also plans to introduce updates to the SMRT Link 10 software that will enable workflow integration to the cloud on Amazon Web Services. Also, a new genome assembly analysis application can generate reference-quality *de novo* assemblies from HiFi reads.

The Sequel IIe comes at a slight premium to the base model, with a list price of \$525,000, compared to \$495,000. PacBio officials said the firm would deliver the first instruments by the end of 2020. "We will initially offer both systems for a period of time, but we expect demand will be heavily in favor of the Sequel IIe," Hickey said. PacBio is prioritizing new sales but will eventually offer existing customers the opportunity to upgrade their instruments, which can be done at a customer's site.

Introduced with the Sequel II platform in early 2019, HiFi reads are accurate enough to detect single nucleotide variants and provide read lengths long enough to detect structural variants. The firm described its [circular consensus sequencing \(CCS\) protocol](#) in a *BioRxiv* preprint in January 2019.

"HiFi is taking the subset of those [CCS] reads with quality above Q20," Hickey said. "The majority end up being 99.9 percent accurate, putting them on par with short reads." On the Sequel II, each read is stored as a subfile, Hickey explained. "You had to use a significant amount of computing capacity just to distill that down into HiFi reads," he said. "You don't need to do that anymore."

Integrated processors from AMD have increased the computing power on the instrument. "We also needed to spend a lot of time optimizing and refactoring code that generates these HiFi reads," Hickey said.

PacBio expects the instrument to change the calculus for existing and potential customers on computing needs. "Previously, the cost of the compute platform to support one instrument was about \$100,000," Hickey said. A computer cluster that works with only HiFi reads could cost only \$20,000, he said, and using cloud services could reduce costs further. Over a three-year project, customers could save more than \$200,000, he estimated. And for customers that have already invested in computing resources, rather than generating HiFi data, "they can use it for more valuable activities like getting the answers to the biological questions they care about," Blethrow said.

PacBio is confident enough in its new product that it is skipping an early-access program "in the interest of expediency," Hickey said, adding that the changes to the user should be minimal. "Really the only change in experience is fewer steps and the waiting you no longer need to do," he said.