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Bio-Rad Expects Expansion of Clinical ddPCR System Menu With FDA Clearance

Feb 22, 2019 | Madeleine Johnson

NEW YORK (GenomeWeb) – With US Food and Drug Administration clearance of Bio-Rad Laboratories' new clinical Droplet Digital PCR instrument and an assay to monitor treatment of chronic myeloid leukemia patients, the company now sees opportunities to rapidly grow the menu available on the clinical diagnostics system. The firm plans to add more oncology tests as well as noninvasive prenatal testing and newborn screening assays through both in-house development and partnerships with third-party assay makers.

The Asia Pacific region – which has been one of the fastest adopters of its Droplet Digital PCR for clinical lab developed testing – is a growing part of Bio-Rad's business, which the firm also believes will see a ripple effect from the first FDA clearance of a clinical ddPCR system.

Bio-Rad launched its first ddPCR system in 2012 and since then there have been more than 3,400 publications citing the technology, including more than 900 publications focused on liquid biopsy.

"We have had a long-standing [digital PCR] business that has been basically pulled into the clinical laboratory," Lisa Jensen-Long, vice president of marketing for the Digital Biology Group at Bio-Rad, said in an interview.

The firm has had CE-IVD approval for the QXDx BCR-ABL %IS Kit since 2017. "That gave us a lot of registration ability in the rest of the world, but there's always a pocket of countries that really don't react until you have IVD approval from the US," Jensen-Long said.

The clinical test quantifies BCR-ABL fusions in CML, specifically p210 transcripts, and is able to detect the residual levels seen in patients on tyrosine kinase inhibitor therapy. This is clinically useful because measuring residual levels of BCR-ABL in patients treated with the first-line TKI imatinib can help physicians decide whether a patient is continuing to respond, or whether a second-line TKI, such as dasatinib, nilotinib, or bosutinib, is needed.

The test was also cleared along with the firm's new clinical instrument, called the QXDx. The new instrument differs in a number of ways from the QX200 research-use-only instrument, Jensen-Long said.

Firstly, it is manufactured in an ISO 13485-compliant facility, and it has been fully verified and validated according to FDA standards.

It also uses unique software that enables users to work with the instrument in a clinical IVD mode or a RUO mode.

The clinical mode has locked workflow settings that are established and validated for the BCR-ABL test, but customers can switch to the RUO mode to develop and run their own workflows or lab-developed tests as well. The software also has other features required for FDA compliance, such as enabling tracing and tracking of reagents and lots.

The QXDx runs between eight and 48 samples for the BCR-ABL test in the IVD mode, Jensen-Long said, but it can still also run a 96-well format, just as the QX200 instrument does, when it is in the RUO mode.

Having an FDA-cleared assay and instrument is expected to now bring new opportunities. For example, Jensen-Long noted that there are some areas in the US and other countries that require labs to purchase cleared tests if they are available, so that is now a new market the firm can enter.

Furthermore, Bio-Rad intends to work with third-party kit developers to help add menu to its clinical system, and having a cleared instrument makes that pathway much smoother for developers.

"Without a registered or a cleared platform, it doesn't really allow third-party entities to be able to put tests or assays onto our platform and send them through the FDA," Jensen-Long said.

She added that the firm is aware of a number of CLIA laboratories who are in clinical trials to submit their applications to the FDA, for example, but Bio-Rad does not have authorization at this time to make them public.

Jensen-Long said that the firm is "open and available to be able to talk about partnerships" and that the details of each one may be unique. For example, in initial discussions some developers have indicated they would like Bio-Rad to be the distributor of their test on the QXDx system, while others have a good distribution system already.

"We are early days in putting those contracts together, so we're really trying to be flexible in our approach to what works for those manufacturers," Jensen-Long said.

In terms of menu development on the QXDx, the firm plans to continue its own focus on the oncology space, Jensen-Long said, but also to expand into other areas.

"We have a pretty broad roadmap within oncology; most of it is unique content that we've been curating with partners around the globe," she said, adding that this work is still in development and specific details haven't yet been disclosed.

Oncology assays that detect residual levels of tumor DNA from liquid biopsies taken during or after cancer treatments, for example, could presumably take advantage of the fact that the ddPCR technology provides absolute quantification of very low levels of target nucleic acid sequences.

But Bio-Rad also sees growing opportunities for clinical ddPCR in NIPT and early infant testing as well. The Digital Biology group is now working with Bio-Rad's Clinical Diagnostics division on NIPT testing and markers for neonatal testing and prenatal testing, Jensen-Long said.

Specifically, the groups have been pursuing spinal muscular atrophy and sickle cell disease testing, both of which are typical tests run on newborns. Jensen-Long said that in addition they are also looking into roughly a dozen other assays for more rare targets that are already in the market as clinical LDTs.

"With an anchor of NIPT testing, it does make sense to commercialize the rest of those tests in an IVD format" as well, she said.

Bio-Rad is also in active discussions with potential partners in the pharmaceutical industry who are using ddPCR for both companion and complementary testing, Jensen-Long said.

Potential ex-US impacts

The rigor and stringency of a US clinical trial seems to resonate with regulators in other parts of the world, Jensen-Long said, and Bio-Rad expects that FDA clearance will now impact its global business, particularly in Asia.

For example, Japan has additional regulations beyond what the US has, "but the weight of a clinical trial in the US allows you to be able to have a much smoother path in Japan," Jensen-Long said.

Richard Harrison, the firm's digital biology marketing manager of the Asia-Pacific region, said that Asia has generally been a very active area for the adoption of digital PCR into *in vitro* diagnostics, and

nations such as India, which has a rapidly growing healthcare market, also take FDA clearance very seriously in their local approval decisions.

To market an IVD test in China requires registration in the test's country of origin as well as in-country clinical trials in China, Jensen-Long said. "We have started trials in China, and we are pretty close to having them finished," she said.

The firm also has a kit manufacturing partner in China that is its submission partner there, and it expects the Chinese National Medical Products Administration — formerly the China FDA — to approve a clinical ddPCR BRAF test on the QXDx system at some point in the next year or so.

Harrison noted that the firm has also seen a lot of success in Taiwan, where digital PCR is being used in a national newborn screening program for SMA testing.

"We're already seeing expansion of that into other regions around Asia as the new drug nusinersen has become available and newborn screening becomes more effective," Harrison said.

In general, Asia was an area where the clinical market adopted the platform very early, Harrison said. The acceptance of clinical ddPCR in Asia — where, he noted, the second instrument Bio-Rad sold was for LDT use in a clinical lab — has also led to opportunities.

"A special feature of the very dynamic Asian business market has been that a very significant number of our third-party partners are from Asia," Harrison said.

Companies may be interested in putting their technology on Bio-Rad's platform because they recognize that digital PCR reduces the variability — between users, sites, days, and instruments — seen in technologies like qPCR and next-generation sequencing, Harrison said.

But beyond benefits to reproducibility, Harrison noted that firms might see a commercial advantage as well. Bio-Rad has structured its program for working with third-party developers in such a way that "it's very amenable to those groups that may not have a huge amount of capital, but do have a great idea," he said.

Essentially, the firm has tried to reduce the barriers to getting to market for these developers. "By having registered platforms in as many markets as we can and a good support structure, they can treat their component as a plug-in to an already-established solution," Harrison said.

Furthermore, adding a test to an instrument with a broader menu may benefit third-party developers of assays that might be more rarely used. "If [users] can adopt a platform that has quite a variety of flexible plug-in tests, we expect that to really begin to accelerate adoption," he said.

With the potential third-party developer content, "The portfolio that is going to be available to digital PCR QXDx users in the medium term will be substantial, beyond what Bio-Rad alone can generate," Harrison said, adding, "These partners are going to be able to bring in areas outside our focus on oncology and precision medicine."

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