India Banks on Decentralized Molecular COVID-19 Testing

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NEW YORK – Decentralized molecular testing is gaining ground for SARS-CoV-2 diagnosis in India. Due in part to a robust anti-tuberculosis campaign, the testing modality has made inroads into the country's complex and tiered healthcare system during the past decade. Now, decentralized platforms from firms like MolBio Diagnostics and Cepheid, as well as newcomer Tata Group, are starting to play a significant role in COVID-19 diagnostic testing in India as well.

As of October 9, India had 6.9 million cases of COVID-19, second only to the US, which had 7.6 million cases. The total number of lives lost to the virus in India is 106,490, third in the world behind 148,957 in Brazil and 213,360 in the US, according to a tracker curated by Johns Hopkins University.

But although the COVID-19 outbreak in India began to take off later than in the US, there are some signs that the country may now be "bending the curve" and reducing transmission.

Sumit Mitra, president of global business for MolBio Diagnostics, based in the state of Goa in western India, himself recently survived severe COVID-induced pneumonia. In an email interview, Mitra said he is happy to be alive. "Progress is slow, but I am very hopeful of making a full recovery," he wrote.

India started its COVID response early in March, Mitra said, with lockdowns and other preparations to fortify the country's healthcare structure for the long haul.

MolBio has contributed to the effort with its TrueLab system, a portable pair of instruments for 20-minute sample prep and three-channel, 40-cycle real-time PCR in 35 minutes, as previously reported. The firm's sample prep instrument is called TruPrep and the real-time PCR instrument is named TruNat.

MolBio was one of the first companies to develop a decentralized SARS-CoV-2 assay, and among the first to launch a test in India.

Mitra said the firm completed two tests — a pan-SARS TrueNat Beta CoV test to detect the virus' E gene and the TrueNat SARS-CoV-2 test to detect the RdRp gene — within a month of the viral sequences' publication by the World Health Organization.

The initial testing algorithm was to screen samples with the E gene, and to confirm positives with the RdRp gene test, Mitra said. These tests underwent intensive evaluation at the National Institutes of Virology in Pune and were then granted approval to market, he said.

MolBio subsequently introduced the TrueNat COVID 19 test, which has both the E and ORF1a genes in a duplex, further simplifying the workflow.

In the past six months, MolBio has deployed more than 2,500 TrueLab platforms in India, in every state, and in both government and private settings, Mitra said.

"While this has provided high technology access to the remotest of areas, it has also unburdened the pressure on central laboratories," he said.

The firm expects the expanded installed base to have long-term effects on its business as well, as it views its point-of-care instrument as a "complete solution" and has developed a large number of infectious disease assays that run on the system.

"The real impact of these installations will be felt when Dengue strikes, [or] when H1N1 strikes," Mitra said, because "India has now created a structure to be proactively ready to test for a variety of vector-borne pathogens, respiratory pathogens, viruses, parasites, and the like."

At least one of MolBio's SARS-CoV-2 tests has already been scrutinized externally. The Foundation for Innovative New Diagnostics evaluated both the MolBio and Cepheid SARS-CoV-2 tests and found that MolBio's E+RdRp SARS-CoV-2 test had sensitivity and specificity of 98 percent and 96 percent, respectively, compared to lab-based RT-qPCR tests from Altona Diagnostics and Seegene. It also reported that compared to the Roche Cobas RT-qPCR test, the Cepheid E gene test target had a sensitivity and specificity of 98 percent and 100 percent, while the N2 gene test target had a sensitivity and specificity of 100 percent and 99 percent, respectively.

Interplay between TB and COVID-19 testing

India has the largest number of tuberculosis cases in the world, and rapid diagnosis and drug resistance detection have been the focus of global efforts in the country.

Decentralized diagnostic testing in particular has been a lynchpin of India's approach to tuberculosis, and the country has incorporated the Cepheid GeneXpert and MolBio TrueNat systems into rapid molecular testing labs as part of the country's National Tuberculosis Elimination Program (NTEP).

Mitra said that because these systems also now support SARS-CoV-2 testing, the government of India has recently highlighted the fact that it is testing for COVID-19 on the same platforms it procured for the NTEP.

A Cepheid spokesperson in India said that the company is currently growing in India and is also actively participating in the country's "Make In India" Initiative, a government program launched in 2014 to spur greater international investment in manufacturing in the country.

Cepheid announced in 2018 that under the Make in India initiative, it would manufacture a portable system called the Edge in the country, for example. Also, Co-Diagnostics, a Salt Lake City-based qPCR it developer, formed a joint venture in India, CoSara Diagnostics, and broke ground late last year on a manufacturing facility in Ranoli in the state of Gujarat that is aligned with the Make in India agenda, as previously reported.

"Our focus with this initiative is manufacturing TB tests," the Cepheid spokesperson said in an email. "We are supplying as many Xpert Xpress SARS-CoV-2 tests as possible, but many locally developed tests are also available." The spokesperson added that while the Cepheid COVID-19 tests are not manufactured in India, the company is vertically integrated, manufacturing its own reagents and not experiencing any shortage of reagents or other components.

Government labs, private hospital labs, and hospitals are the Cepheid's main customers across the country. "We have seen an increase in demand for our instruments, due to both TB and COVID, as the same instrument can be used to run any of our tests," the spokesperson said.

TB will remain a priority for Cepheid and the firm is "committed to supplying the requirements for India," but Cepheid India has also worked closely with the government and private segment "to ensure supplies of COVID tests based on availability," the spokesperson said.

MolBio also has a significant footprint in decentralized TB testing in India, and in July of this year, the WHO endorsed three of its TrueNat tests for the detection of TB and drug resistant strains.

While TB-related instrument placements could enhance access to COVID-19 testing, in a recent article in the *Journal of Clinical Microbiology,* authors from FIND and elsewhere expressed concern that diseases like TB will be neglected during the COVID-19 pandemic. They cited modeling from the Stop TB Partnership that suggested pandemic-related lockdowns would lead to 1.5 million excess TB-related deaths between 2020 and 2025.

"One clear area for intervention is the integration of TB and COVID-19 testing," the authors wrote. Patients with either disease may have a cough, fever, or difficulty breathing, they wrote, and this represents an opportunity to test presumptive patients for TB and COVID-19 in one clinical encounter. They also said that dual testing would be more convenient for patients and healthcare workers, as it could reduce the number of necessary follow-up visits.

The study said that the recently launched Xpert Xpress SARS-CoV-2 cartridge might allow low- and middle-income countries to increase their capacity to test for COVID-19, for example, as many countries already have existing Cepheid GeneXpert networks.

But the authors noted concerns that a ramp-up of COVID-19 testing on the GeneXpert system may come at the expense of TB testing in low- and middle-income countries that rely on Xpert MTB/RIF.

"Abbott and Roche also have released COVID-19 assays to run on their centralized testing platforms ... Both systems are used in some reference laboratories of countries with high TB burden for multi-disease testing," the authors wrote. Leveraging existing multi-disease nucleic acid amplification testing platforms for both TB and COVID-19 testing could be an effective strategy going forward, they concluded.

There are as many as 50,000 laboratories in India, Mitra said, including government and private labs, such as those at corporate hospitals, nursing homes, and laboratory chains.

The government of India has currently installed more than 1,000 TrueNat systems, including in very remote states, he said, and the instrument is also being used for routine testing by the Army, Navy, and Air Force of the country. The firm has also installed more than 1,500 systems at private labs in India.

The platform has been taken up internationally as well, by the United Nations with contracts for their global field missions and UN-International Oversea Migration (IOM) programs, Mitra said, and the firm is also in discussions with Doctors Without Borders.

In the first six months of the pandemic so far, increased uptake of TrueNat has led to financial growth that MolBio has already reinvested into a state-of-the art manufacturing facility in Goa, Mitra said, that will augment production capabilities fivefold.

In addition to impacting decentralized systems, the coronavirus pandemic is also fueling research and development in India on new technologies.

One recent entrant to the space is a CRISPR-based test licensed from India's Council of Scientific and Industrial Research Institute of Genomics and Integrative Biology (CSIR-IGIB) by Tata Medical and Diagnostics, a two-month-old subsidiary of global conglomerate Tata Group.

The test system is called FNCAS9 Editor-Limited Uniform Detection Assay, or Feluda, in honor of a fictional Bengali detective. Much as detective Feluda is an admirer of Sherlock Holmes, the Feluda system has some parallels with a CRISPR-based system from Sherlock Biosciences, as well as with systems from Mammoth Bioscience and others.

The Sherlock and Mammoth systems have obtained US Food and Drug Administration Emergency Use Authorization for SARS-CoV-2 tests, while the Feluda assay received regulatory authorization from the Drug Controller General of India in September. Tata Group did not reply to a request for comment in time for publication.

Feluda testing reportedly takes 45 minutes and uses a CRISPR readout with paper strips, similar to technology in development in the US from CRISPR diagnostics startup Caspr Biotech and perhaps reflective of a general growing interest in paper-based testing.

With respect to Feluda, MolBio's Mitra said the firm has always welcomed the entry of new products into the space. On the other hand, it is also aware of the challenges in translating a technology from a research and development stage to a market-ready product. The system will likely need additional menu to be successful, he said, but overall "the market is ever expanding for everyone to make their mark."

Large diagnostics labs in India use products from Abbott, Roche, and Hologic, Mitra noted, but decentralized testing does not really compete with the large lab-based instruments. "Settings where the workloads are very heavy will be best served by the large-throughput systems from [these] companies," he said.

Mitra noted that the complexities of the healthcare system in India require global companies to take a long-term view to their investment there.

"India is a country where besides real science, you would need patience to build the market," he said. "Hopefully, these companies will remain invested even if their immediate returns may not look too encouraging."

Overall, Mitra said, he believes that because of the pandemic, the value of decentralized molecular testing — particularly with the MolBio system — will soon be even more appreciated in India, and perhaps globally as well.

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