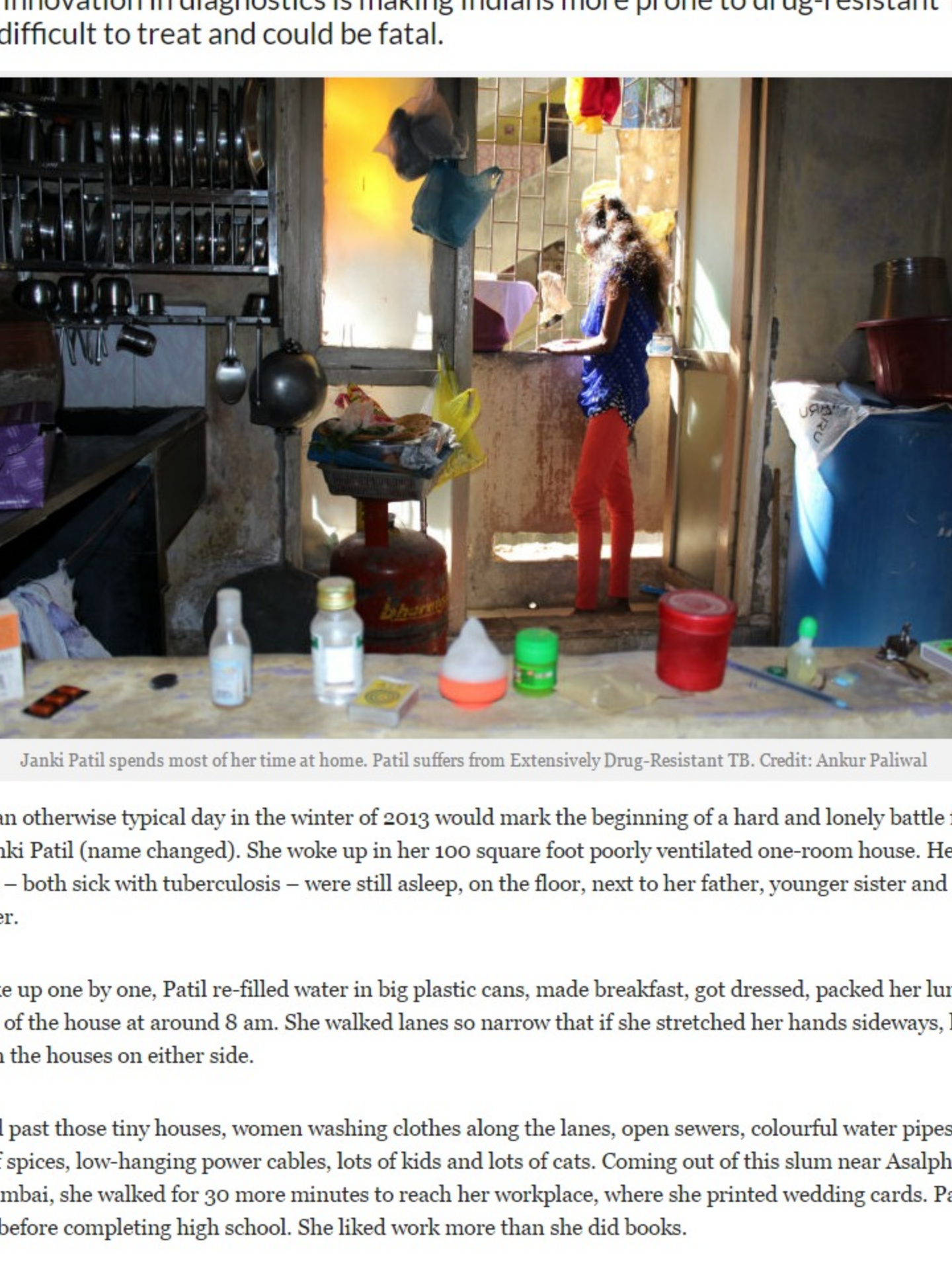
FEATURED

In India's Fight Against Tuberculosis, Diagnostics Remains Poorly Understood

BY ANKUR PALIWAL ON 03/03/2017 • LEAVE A COMMENT

A lack of innovation in diagnostics is making Indians more prone to drug-resistant TB, which is difficult to treat and could be fatal.



Janki Patil spends most of her time at home. Patil suffers from Extensively Drug-Resistant TB. Credit: Ankur Paliwal

The end of an otherwise typical day in the winter of 2013 would mark the beginning of a hard and lonely battle for 18-year-old Janki Patil (name changed). She woke up in her 100 square foot poorly ventilated one-room house. Her brother and mother – both sick with tuberculosis – were still asleep, on the floor, next to her father, younger sister and grandmother.

As they woke up one by one, Patil re-filled water in big plastic cans, made breakfast, got dressed, packed her lunch and stepped out of the house at around 8 am. She walked lanes so narrow that if she stretched her hands sideways, her fingers would touch the houses on either side.

Patil walked past those tiny houses, women washing clothes along the lanes, open sewers, colourful water pipes, strong fragrance of spices, low-hanging power cables, lots of kids and lots of cats. Coming out of this slum near Asalpha in western Mumbai, she walked for 30 more minutes to reach her workplace, where she printed wedding cards. Patil had left her studies before completing high school. She liked work more than she did books.

Late evening, when Patil was home watching TV, sudden acute pain hit the left side of her chest. She rushed to a family physician who prescribed a few medicines and an X-ray. A day later, when the physician – who was aware of the Patil family medical history – saw her test report, he suspected TB.

He referred her to a chest specialist who diagnosed that Patil had a traditional, easily treatable kind of TB. Little did Patil know that she would soon be sucked into a health system where delayed diagnosis, misdiagnosis and use of inefficient diagnostics can make patients like her prone to fatal drug-resistant forms of TB.

Three years later, and even after thousands of medicines and over a hundred injections, Patil suffers from extensively drug-resistant tuberculosis, XDR-TB, in which the notorious tuberculosis bacteria in her body are unaffected against most available anti-TB drugs. Only 28% of XDR patients who begin treatment get cured.

While India houses the largest number – 27% – of the world's 10.4 million new TB patients, Mumbai is the epicentre of the disease in the country. The metropolis has many overcrowded slums where about five people share a house like that of Patil's. Such spaces are ideal for the TB bacteria to spread.

At 79,000, India also has the highest number of multi-drug resistant, or MDR-TB, patients who don't respond to the two most powerful TB drugs. Drug-resistant TB has a range from less severe to more severe forms – all fatal if untreated – depending on how resistant the TB bacteria are against the 13 anti-TB drugs.

Even traditional TB is fatal if left untreated. Drug-resistant TB mostly results from indiscriminate use of anti-TB medicines. It is costlier and harder to treat than the traditional form. Patients have to undergo a two-year long treatment with drugs so toxic that several even end up dropping out.

What's more troubling is that the number of severe drug-resistant forms is rising. A 2015 study that looked at drug-resistance pattern in patients in Mumbai between 2005 and 2013, found that while multi-drug resistant TB cases were dropping, the worse forms, like pre-XDR TB and XDR-TB, were increasing. As many as 57% patients in the sample had pre-XDR TB. "That was worrying," said Alpa Dalal, a TB and chest physician in Mumbai, who was part of the study. The trend continues.

Vikas Oswal, a TB physician who attends to patients at three different centres in the most TB-affected areas of Mumbai, points to something even more worrisome. People who never had TB are directly getting drug-resistant strains from their affected family or community. The youngest among such cases that Oswal has is an 11-month-old who will have to endure drugs for two years.

One effective way of controlling TB is early and correct diagnosis, which increases the likelihood of a patient getting timely and correct treatment. A recent study co-authored by Nerges Mistry of The Foundation for Medical Research in Mumbai, shows that there is an average delay of 60 days before a patient gets diagnosed, with both patients and doctors responsible for the delay. Patients waste about three weeks ignoring symptoms and trying to self-medicate before approaching a doctor. The doctor then wastes about five weeks in diagnosing a patient. In case of MDR-TB, the delay in diagnosis is close to three months from the time a patient first approaches a doctor. "Doctors keep giving symptomatic treatment using antibiotics without asking for a test," said Oswal.

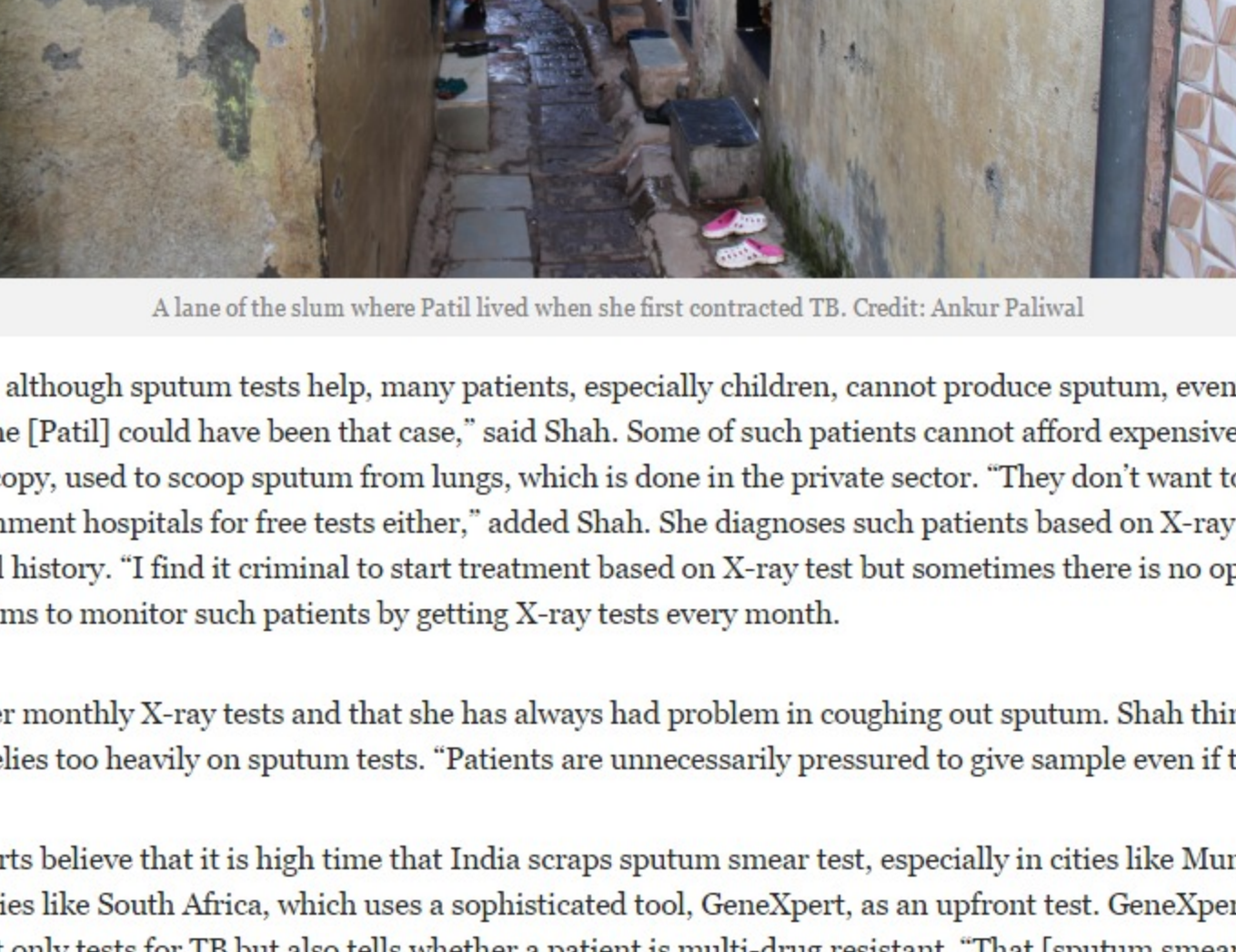
Another 2016 study, in which researchers interviewed over 100 general physicians of varying qualification in Mumbai and Patna, confirms Oswal's point. Most doctors continued to treat their patients by changing antibiotics because they believed that their patients needed treatment more than testing. "I will not think about TB before my regimen fails," said a doctor in the study. Patients also switch doctors if their condition doesn't improve. The new doctor might start the same treatment again. Meanwhile, patients roam around infecting people in their family, neighbourhood, workplace and in the mass transport until they are diagnosed and put on the right treatment.

"Unfortunately, the trend in our medical community is more towards treatment and less towards diagnosis," said Dalal. The practice is rampant in the unregulated private sector where about 50% TB patients seek care. In Mumbai, PATH, an international non-profit, is working with city administration to educate private physicians about correct TB diagnosis and treatment.

§

Patil's physician had referred her to Tejal Shah, a chest physician who runs a private clinic in Mumbai's Ghatkopar area. At that time, Shah had already been treating Patil's brother and mother for about a year. Patil recalls that Shah started her treatment after checking her X-ray report. "She didn't ask for any sputum based test," said Patil.

According to Revised National Tuberculosis Control Program guidelines, a patient suspected of having TB should undergo a sputum smear test to confirm whether or not the patient has the disease. The X-ray test can be used to further confirm TB but not as an upfront test. Diseases like bacterial pneumonia and bronchitis can look like TB on an X-ray report.



A lane of the slum where Patil lived when she first contracted TB. Credit: Ankur Paliwal

Shah said that although sputum tests help, many patients, especially children, cannot produce sputum, even after assistance. "She [Patil] could have been that case," said Shah. Some of such patients cannot afford expensive techniques like bronchoscopy, used to scoop sputum from lungs, which is done in the private sector. "They don't want to queue up in front of government hospitals for free tests either," added Shah. She diagnoses such patients based on X-ray test and family medical history. "I find it criminal to start treatment based on X-ray test but sometimes there is no option," she said. Shah claims to monitor such patients by getting X-ray tests every month.

Patil recalls her monthly X-ray tests and that she has always had problem in coughing out sputum. Shah thinks that the government relies too heavily on sputum tests. "Patients are unnecessarily pressured to give sample even if they cannot."

Some TB experts believe that it is high time that India scraps sputum smear test, especially in cities like Mumbai, and follows countries like South Africa, which uses a sophisticated tool, GeneXpert, as an upfront test. GeneXpert, with 80% sensitivity, not only tests for TB but also tells whether a patient is multi-drug resistant. "That [sputum smears] is a stone age test in the molecular age," said Zarir Udwadia, chest physician with P. D. Hinduja National Hospital and Medical Research Center in Mumbai. "When we know the extent of MDR TB, GeneXpert should be made as frequently available as your damn ATM machines," said Udwadia, perhaps the most vocal doctor against the TB menace in the country.

"The test misses about half of the TB cases," said Madhukar Pai, the director at Global Health Programs at McGill University in Canada. "India is in a great need to upgrade its diagnostics." Even in 2016, sputum smear microscopy was the most widely used diagnostic tool in low and middle income countries. A study that used GeneXpert as an upfront test found that TB case detection increased by about 40% and MDR notification increased five fold. "You will save a lot of time and thereby save transmission," said Udwadia.

Pai said that it will be difficult for India to meet its end TB goal if it continues to rely on sputum smears. Sunil Khaparde, the deputy director general of TB division in the health ministry, thinks otherwise. "Sputum smear tests are easily accessible to patients," he said. "If a test report is negative and the patient still has symptoms, the sample can directly be sent for GeneXpert testing." Upfront GeneXpert is done only for patients with extrapulmonary TB, HIV patients who also have TB and children. Sputum sample from patients with traditional pulmonary TB is tested for GeneXpert only if their sputum smear report is positive even after two months of TB treatment. "You also have to see the cost effectiveness of putting GeneXpert everywhere," said Kharparde. Government of India spends about 1% of its GDP on health, which is among the lowest in the world.

Moreover, access to sputum smear tests isn't as easy as Khaparde thinks. Consider this – Udgir village, where about 1,200 people live, sits atop a mountain and beyond a forest in Kolhapur district that is about 400 kms south of Mumbai. Kolhapur has over 200 cases of MDR-TB and ten cases of XDR-TB.

Udgir is 40 kms away from the nearest lab where sputum smear test is done. The road between the lab and Udgir is so terrible that it took me two hours to reach there. During that time, only one motorbike passed by me in the name of traffic. Ashwini Ramesh, a frontline health worker in Udgir, said that she cannot travel to the lab even if she collects the sputum sample. "There is no public transport and I don't have a personal vehicle," Ramesh said. At the lab, the technician Jayashree Gawli receives about 50 sputum samples a months. Half of them are just saliva that tests negative. Sometimes the sample reaches Gawli so late that it spoils on the way. "I often ask for repeat samples. Sometimes I get, sometimes I don't," said Gawli. The distance between Gawli's lab and the district hospital where the GeneXpert machine is kept is another 70 kms. "It would work really well if we could test the patients where they are," said Ganesh Patil, Kolhapur district coordinator with Population Survey International, a non-profit headquartered in Washington DC.

Although GeneXpert has revolutionised TB diagnosis, it has its limitations. The machine requires consistent power supply and an air conditioner, which is a remote thought in far-flung electricity starved areas of India. As a result, the penetration of all the 628 GeneXpert machines in the public sector is only till the district hospitals. To overcome this challenge, Cepheid, the company that made GeneXpert, will soon pilot GeneXpert Omni, which is portable, rugged and can run on battery the whole day. Its performance, however, is yet to be seen.

Cost is another barrier. Government hospitals where the test is conducted for free are overloaded with samples. In the private sector, the test costs at least Rs 2,000. And, the problems associated with quality sputum sample persist even in the case of GeneXpert. "Almost all of the innovation in TB diagnosis has been around the tests that are done after a sputum sample is submitted," said Jennifer Furin, lecturer on Global Health and Social Medicine at Harvard Medical School. "Lot of work is going on looking at serum and urine "biomarkers" but so far nothing is anywhere near clinical testing." Furin continues, "It is a real shame that the diagnostics lag so far behind in case of TB. "Look at HIV or Ebola where effective, point of care tests were developed so quickly. We should be capable of doing the same thing with TB. But I think a great deal of this lack of innovation is caused by the traditionalist approach."

Agreeing with Furin, Pai said "We need simpler, non-sputum based, point-of-care test." But till then, India should implement the best we have today, said Pai. GeneXpert works best as a screening tool to separate drug-resistant TB patients. Shah agrees that Patil should have undergone GeneXpert when she first approached her. "I am learning from my mistakes. Now I try my best to prove TB before relying on X-ray reports."

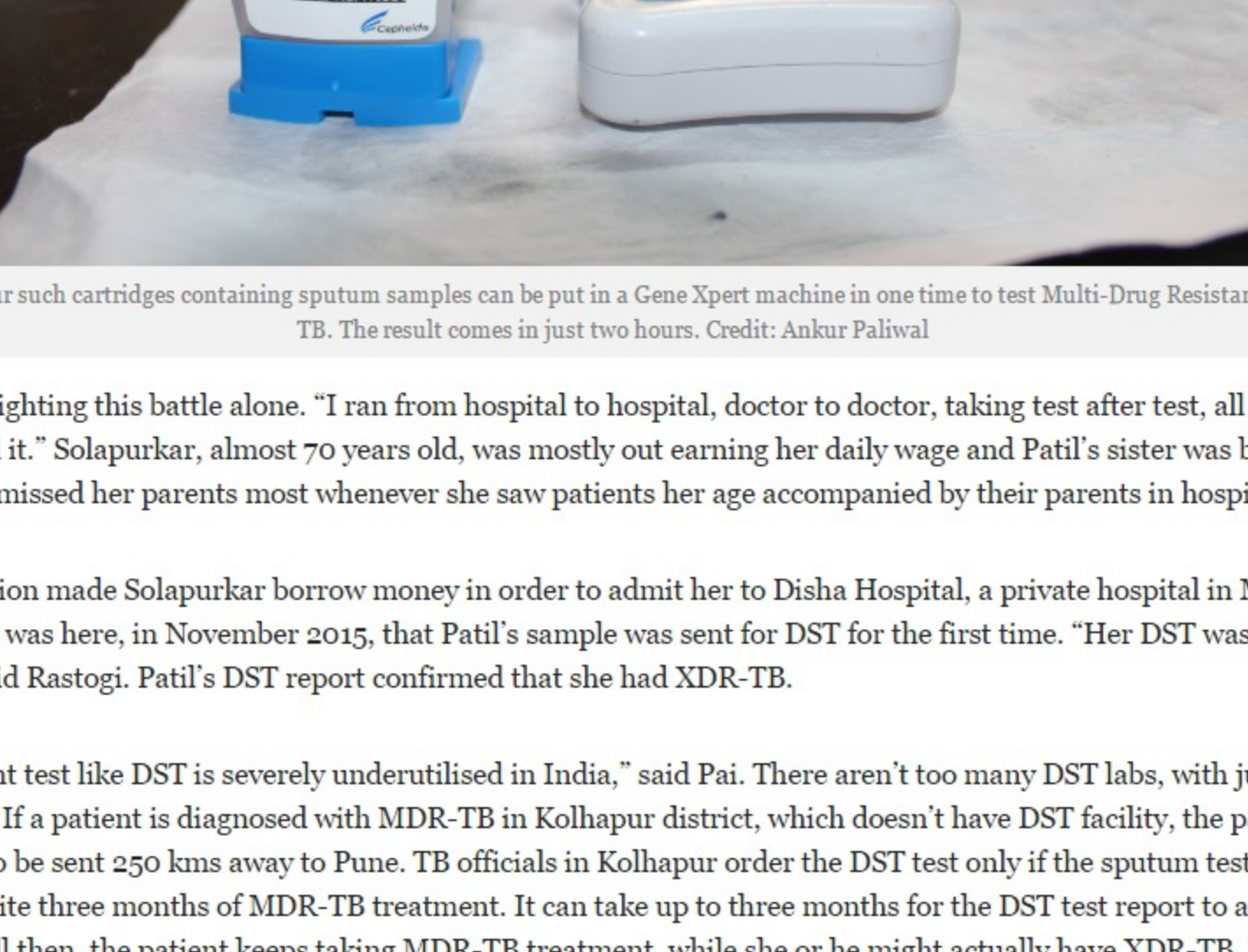
§

During the year Patil was undergoing treatment at Shah's clinic, her mother succumbed to TB, and her father and grandmother passed away. She moved to the house of her maternal grandmother, Bharati Solapurkar (name changed), with her sister. Patil had started to feel better. A few months after the end of her year-long treatment, just when she began to think about going back to work, the pain struck the left side of her chest again.

Worried, she rushed back to Shah who wrote a bunch of tests including GeneXpert, which confirmed that Patil had MDR-TB. It is unclear how Patil got MDR-TB. Realising that she will not be able to afford the treatment, which cost around Rs 2.5 lakhs, Shah referred Patil to Sewri TB hospital, a government hospital in Mumbai, to avail free treatment.

Patil doesn't have good memories of that hospital. After waiting for several hours at the hospital, when her turn came, she didn't like how doctors behaved with her. "They were rude and kept telling me stay away, stay away, sit here, sit there," she recalls. But the doctors started her MDR-TB treatment. Although this treatment lasts for about two years, Patil dropped out after nine months because she didn't feel any better. "Her treatment regimen was not exactly the one that she probably required," said Sarthak Rastogi, chest physician with Medicines Sans Frontiers's (MSF) TB clinic in Mumbai where Patil is currently undergoing XDR-TB treatment. "Probably her resistant pattern was worse than MDR at that time," said Rastogi. Drug susceptibility testing (DST) at that time would have helped Patil's case, but it was not done. The DST tells which drugs will work on the patient and which won't, in other words, the severity of TB. This information helps a doctor customise a treatment regimen. Ideally, a patient's sputum sample should be sent for DST when she or he is diagnosed with MDR-TB.

Patil's health kept deteriorating. She felt too exhausted to speak, spent all her time in bed and needed assistance to use the washroom. By this time Patil and Solapurkar had started to feel frustrated because there was no improvement despite taking so many medicines. "One day *naani* [grandmother] lashed out saying that we better not go anywhere, if you have to die, you will die here only," Patil recalls. "I also thought that I will die."



Four such cartridges containing sputum samples can be put in a Gene Xpert machine in one time to test Multi-Drug Resistant TB. The result comes in just two hours. Credit: Ankur Paliwal

Patil recalls fighting this battle alone. "I ran from hospital to hospital, doctor to doctor, taking test after test, all alone," she said. "I hated it." Solapurkar, almost 70 years old, was mostly out earning her daily wage and Patil's sister was busy with school. Patil missed her parents most whenever she saw patients her age accompanied by their parents in hospitals.

Patil's condition made Solapurkar borrow money in order to admit her to Disha Hospital, a private hospital in Mumbai, for a week. It was here, in November 2015, that Patil's sample was sent for DST for the first time. "Her DST was ordered very late," said Rastogi. Patil's DST report confirmed that she had XDR-TB.

"An important test like DST is severely underutilised in India," said Pai. There aren't too many DST labs, with just 67 across India. If a patient is diagnosed with MDR-TB in Kolhapur district, which doesn't have DST facility, the patient's sample has to be sent 250 kms away to Pune. TB officials in Kolhapur order the DST test only if the sputum test report is positive despite three months of MDR-TB treatment. It can take up to three months for the DST test report to arrive in Kolhapur. Till then, the patient keeps taking MDR-TB treatment, while she or he might actually have XDR-TB. "The process of universal DST will take time," said Khaparde.

Patil's DST report showed that only two out of 13 available drugs worked for her. She needed customised treatment using one or both of the new drugs, Bedaquiline and Delamanid. An effective regime contains at least four working drugs. Both the new drugs are hard to access. While Bedaquiline, strictly regulated by the government, is available in just six cities, including Mumbai, Delamanid is not even registered in India. It can only be accessed through a lengthy process called compassionate use, in which a doctor has to write to the drug maker, Otsuka Pharmaceuticals in this case, requesting it to make the drug available because the patient has no other option left but to take that drug. It is up to the drug maker to provide the drug or not. Bedaquiline can also be accessed through compassionate use. Recently, health activists wrote to the government to direct Otsuka Pharmaceutical to register the drug in India. Currently, about 60 XDR-TB patients have access to Delamanid. There are over 3000 XDR-TB patients in India.

Bedaquiline was yet to be rolled out by the government when Patil was at Disha Hospital. Realising that the available treatments were ineffective and costly for Patil, doctors referred her to MSF's TB clinic in Mumbai that provides free treatment to patients like Patil. However, given the limited resources, the non-profit can only treat a few patients. Currently, 72 patients are enrolled at the clinic. It is a miniscule number given the size of the problem.

Patil visited MSF's clinic in January 2016. "She could barely walk or talk," recalls Rastogi. "Her lungs were extensively damaged." MSF applied for Delamanid, which arrived in June. Meanwhile, she took drugs that helped her get by. After June, Patil's health started to improve. Her recent sputum test report was negative, but her treatment must continue till two years for a complete recovery. "Even after her treatment ends she might not be able to recover her lung functions fully," said Rastogi. "Like she might not be able to run and catch a train like us."

Patil says that she feels much better. She is gaining weight. She often visits her relatives in the city. At home, her favourite way to pass time is to stand near the window of her house and watch the boys play cricket outside. "I like it when they make noise," she said.

Patil has a long road ahead. The Delamanid, which was sent to her in a six-month dose, is about to run out soon. Doctors at the MSF clinic were weighing different options, including reapplying to Otsuka Pharmaceuticals for compassionate use, when I last spoke to them.

After her two-year-long treatment gets over, Patil would like to go back to school. "Earlier I didn't like to study. Now I feel good education will get me a good job," said Patil. "I will be able to take the burden off my grandmother."

The reporting of this story was supported by the MSF Media Fellowship.

Ankur Paliwal is a freelance science and health journalist based in New Delhi.