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What’s eating you?

Superfast tests for microbes could save thousands of lives. Debora MacKenzie reports
Evan Frustaglio was a healthy 13-year-old when he developed a sore throat and fever one Friday. By Sunday his symptoms were worse, so his parents took him to a walk-in clinic. The doctor didn’t prescribe any medications. On Monday Evan collapsed in his father’s arms. He never regained consciousness. It turned out he had swine flu, which was widespread at the time. The drug Tamiflu might well have saved him.

This case was not a one-off. Every day millions of people go to clinics and hospitals seeking treatment for some kind of infectious disease. Most often these are respiratory infections, and their symptoms can be identical whatever bacterium or virus is to blame. Usually the best doctors can do is make an educated guess about which bug is responsible. In many cases it doesn’t actually matter if they get it wrong, because our immune systems will kill off the offending germ.

But it can matter a lot. Not only are life-threatening infections sometimes missed, but even when it is clear that someone’s life is in danger, it can take days or even weeks to identify the cause. The delay means that a person might not get treatment that could have saved them.

For example, it is thought that many of the 250,000 people who die of blood poisoning in the US each year could be saved if the bacterium responsible was identified and appropriate treatment given early. On the other hand, giving antibiotics encourages antibiotic-resistant superbugs to emerge – and thus harms people indirectly.

It doesn’t have to be this way, not any more. More flexible tests

There are already faster tests around. Over the past decade, many new dipsticks have become available that change colour to signal when specific molecules are present, just as in pregnancy tests. They have one major limitation, though. “They’re great at detecting the antibodies a patient makes to an infection, but those don’t appear for weeks, a bit late for many diseases,” says Rosanna Peeling, head of diagnostics at the London School of Hygiene and Tropical Medicine. “What we really want is something like the tricorder on Star Trek. You could point it at anything and it would say what it was.”

Thanks to the revolution in DNA technology, devices that work a bit like that already exist. They have yet to reach hospitals, though. At the moment, the diagnostic DNA tests hospitals use look for just one kind of virus or bacterium. They use a method called PCR to reveal if a specific sequence is present in a sample.

This is useful if you already know what the patient has and you want to see if a
One way to diagnose infections fast might be to literally sniff them out. Bacteria emit a range of volatile chemicals that are characteristic of particular strains. Animals - and even some veteran bacteriologists - can learn to identify these smells. A company called iSense, based in West Palm Beach, Florida, is now trying to develop an artificial nose, based on arrays of dyes that change colour in the presence of certain chemicals. The method can already identify some bacteria growing in culture, and the aim is to identify diseases directly from people's breath, starting with TB.

This is not the first attempt to use arrays of dyes to detect infections. Since the 1980s, researchers have been developing chips that use different chemicals - and especially DNA - to identify pathogens. Most microarrays currently find only one pathogen at a time. But testing for a single sequence. As a result, while reverse transcriptase polymerase chain reaction, or RT-PCR, is more sensitive than the standard, single PCR, it is not great at identifying the cause of an infection. Carrying out dozens of separate DNA tests is prohibitively expensive - and there are around 1400 different kinds of viruses and bacteria that can infect people.

The other obvious problem with single tests is that they can only find the germ they are designed to detect. Yet in cases of flu, for instance, secondary bacterial infections can be lethal. So Ian Lipkin of Columbia University in New York has developed a variant of PCR called MassTag that can look for up to 30 different sequences, and thus up to 30 bugs at once.

Unfortunately, it is less sensitive than testing for a single sequence. As a result, while MassTag and tests like it have been approved for monitoring the spread of infections in the community, they are not yet approved for diagnosing individual patients. "The US Food and Drug Administration won't approve it if it is less sensitive than the standard, single PCR, despite its greater breadth," Lipkin says.

That greater breadth is needed. Joseph DeRisi of the University of California, San Francisco, tells of a 28-year-old woman who went to hospital coughing up phlegm and blood. Soon she was fighting for her life on a respirator. No positive results came out of $100,000 worth of tests; no cultures, even of lung tissue, grew anything. DNA tests for 28 pathogens came up negative.

After a week, desperate doctors sent DeRisi a sample. His team has developed a wide-ranging test using a microarray - a slide with strands of viral DNA, termed probes, attached to it. The sample is washed over it and any DNA in the sample that matches a probe will bind to it. An early version of DeRisi's Virochip helped identify a new kind of coronavirus as the cause of SARS. The latest version has 60,000 probes from more than 1500 viruses. Lipkin has developed a similar array, the GreeneChip, that also looks for bacterial, fungal and parasite DNA.

In a few hours, the Virochip came up with an answer - the woman had the parainfluenza 4 virus. Because it usually causes only mild colds, there are no standard tests for it and, as with most viruses, no treatments. The woman eventually fought it off.

In this case, then, identifying the pathogen did not help. The woman was even given antibiotics as a precaution despite the evidence that a virus was responsible. "It would be a brave clinician who withheld antibiotics from a patient on a respirator just because a particular virus was discovered," says Graham Cooke of Imperial College London.

Of course, the test might have been a lifesaver had it revealed an infection for which we have a treatment. What's more, if such testing becomes routine, it will give companies a reason to develop treatments - you cannot sell drugs against a particular germ if there is no way to tell who is infected in time for the treatment to make difference. But testing will only become routine if the tests are cheap and easy to perform.

So far both DeRisi's and Lipkin's arrays require complicated processing and take 12 to 24 hours to give a result.

Those working on microarray-based tests believe they can be made cheaper and quicker. So far, however, they are achieving this at the expense of breadth. The only microarray approved by the US Food and Drug Administration so far, the Luminex xTAG, can identify just 12 respiratory viruses. It is not clear if really big arrays that can identify rare or novel pathogens will ever overcome the technological and regulatory hurdles needed to reach the clinic. The FDA has not even told companies what evidence it needs to approve such devices for clinical use, says Charles Chiu, who works with DeRisi on the Virochip. In theory, the sensitivity and specificity of each probe needs to be tested, but this is impossible with tens of thousands of probes.

Although big arrays cannot be used for routine diagnosis, they can be used to solve occasional medical mysteries, reveal what pathogens are circulating and screen blood or drugs. Yet even the biggest arrays don't always produce an answer. When Lipkin recently used GreeneChip to try to find out what had killed three people who all received organ transplants from the same donor,

"Twice we’ve identified a new disease – swine flu and the cause of SARS. Yet our approach remains unapproved"
it found no matches.

Lipkin then resorted to sequencing all the RNA in samples from one victim, yielding 100,000 sequences in all. Heavy-duty computer processing revealed that 14 of them came from a new arenavirus, a kind of virus more usually seen in rodents.

This “sequence everything” approach, known as metagenomics, had previously been used to identify which viruses and bacteria lurking in seawater, for instance, but until recently it was far too time-consuming and expensive to be worth considering when looking for the cause of diseases. The beauty of the approach, though, is that it can reveal in glorious detail exactly which microbes are present, even if they are unlike anything seen before. In the case of bacteria, it can even reveal which genes conferring resistance to antibiotics are present and thus which antibiotics won’t work. And the technology is advancing fast: “I think we are maybe five years from the point where we could use sequencing for routine pathogen diagnosis,” says Chiu. “The question now is whether we will go to microarray first, or just straight to that.”

Or maybe another method will beat them both. “Sequencing isn’t fast and cheap enough yet,” says Ecker of Ibis Biosciences, recently renamed PlexID after it was bought by US-based pharmaceutical giant Abbott. “Our machine costs $400,000, but each test costs little, so it’s effective for a big hospital lab.”

His company’s approach works by making lots of copies of any DNA characteristic of a wide range of viruses, bacteria or fungi. Then a mass spectrometer determines the mass of the amplified DNA fragments, which varies depending on their length and composition. The result is a library of characteristic molecular fingerprints that can be used to identify the pathogen – even if the disease it causes has not been seen before.

In 2003, the company also correctly identified a kind of coronavirus as the cause of SARS. In 2009, it spotted a new flu virus in a boy at the US-Mexican border – the first diagnosis of swine flu in the US. “That’s twice we’ve identified a new disease when it wasn’t a drill, it was the real deal,” says Ecker. Yet you cannot even look at the PlexID website without clicking on a “not for use in diagnostic procedures” disclaimer. To impress the FDA, PlexID must prove its technique is as good as culturing the pathogen, which remains the gold standard. “The trouble is, we’re more sensitive,” says Ecker. When PlexID finds pathogens in a sample and culturing doesn’t, Ecker must prove PlexID has got it right.

“Introducing a game-changing technology is always going to take time,” says Ecker. The company is applying for approval to diagnose flu, then wants to go for a set of respiratory infections, and after that a broad spectrum of viruses, bacteria and fungi. Yet that is far less than the technology can do – and falls short of what is needed. What’s more, if the technology does take off, Ecker thinks economies of scale could eventually bring costs down to the point that doctor’s clinics could afford it.

Will doctors want it? Some might see such tests as a threat, but they are no replacement for doctors. “We’ll still need their judgement based on the patient’s history and symptoms,” Ecker says. Tests may identify a microbe that isn’t the cause of the disease or it might pick up several, only one of which is problematic. And diagnosis is just the start of treatment.

Chiu is optimistic about the prospects for the technology. “The new generation of medics is tech-savvy,” he says. “Medicine is crying out for this: if it works, they’ll want it.”

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