The FibroScan device is a non-invasive tool that uses ultrasound to detect liver fibrosis.

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DIAGNOSTICS

Missing the point

Conventional detection of advanced fatty liver disease relies on biopsy. Less onerous methods may help to save lives.

BY MICHAEL EISENSTEIN

To a person who is experiencing no obvious signs of illness, the idea of having a hole punched in their liver is a hard sell. The hole is tiny — just the diameter of a hollow needle — and such biopsies remain the hepatologist's only reliable tool for directly assessing the clandestine damage inflicted on the liver by non-alcoholic steatohepatitis (NASH). NASH is the advanced and severe form of non-alcoholic fatty liver disease (NAFLD), a condition linked with obesity and diabetes. Yet a number of people still shy away from the procedure owing to concerns about safety and discomfort.

"A lot of patients say that they don't want a biopsy and that they'll try to lose weight first," says Michelle Lai, a gastroenterologist at Beth Israel Deaconess Medical Center in Boston, Massachusetts. "Then they come back and haven't lost weight, and we see that the risk to their liver has risen." The biopsy procedure is generally safe, but the rare complications that occur can be severe, including uncontrolled bleeding from the liver — and even death, for an estimated 1 in 10,000 recipients.

Liver biopsy is also not well suited to the task of tracking a condition that is so pervasive and difficult to detect, in which many people at risk remain largely without symptoms until the onset of severe scarring (cirrhosis). Laurent Castera, a hepatologist at the University of Paris Diderot's Beaujon Hospital in Clichy, France, estimates that as many as 25% of his country's population have some form of NAFLD. "There are not enough hepatologists in France to perform these liver biopsies," he says, "and even fewer pathologists who could interpret them."

This leaves physicians in a bind, but non-invasive alternatives are emerging. None is yet sophisticated or robust enough to routinely deliver the confident diagnostic 'yes' or 'no' that a biopsy can provide. However, these methods are giving clinicians a faster and more palatable means of performing triage on people with a high risk of developing NASH. And they could even help to realize the goal of implementing large-scale, community-wide screening to intercept the condition long before it develops.

STIFF RESISTANCE

The main hallmark of NAFLD is steatosis — the accumulation of fat in the liver. Some people with the condition also acquire hepatic scar tissue, through a process known as fibrosis. Many never progress past this stage, but those who go on to develop NASH will experience damaging inflammation and worsening fibrosis. This can lead to cirrhosis and liver failure, although the timely detection of advanced fibrosis can help to bring livers back from the brink. "Even early in cirrhosis, if you really lose a lot of weight, there's still some chance of reversal," says Lai.

Over the past 15 years, a growing number of clinicians have used a non-invasive tool called FibroScan to detect liver fibrosis. FibroScan is based on a technique called transient elastography, in which ultrasound is used to determine the stiffness of the liver. "It's a point-of-care technique that's widely available and easy to use," says Castera. Transient elastography correctly identifies cirrhosis at least 90% of the time, but Castera says that FibroScan is better at ruling out severe fibrosis or cirrhosis than at making a positive diagnosis.

For less serious diagnoses, transient elastography can yield unreliable results. In some cases, this is due to other physiological factors that affect liver stiffness, including a severe build-up of fat — or even just having a meal before the scan. Of particular concern is that the tool performs poorly in people who are at especially high risk of developing NAFLD. "The test fails as body mass increases," explains Rohit Loomba, a gastroenterologist at the University of California, San Diego. "When you have people with a body mass index of 40, the test is of limited value." He notes that this could be problematic for the United States, which has one of the highest incidences of obesity in the world. An updated version of the FibroScan probe seems to partially overcome this issue.

For greater accuracy, Loomba favours an approach that uses a conventional magnetic resonance imaging (MRI) scanner to map

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the extent of fibrosis throughout the liver. The approach, known as magnetic resonance elastography (MRE), "is probably the best for detection of advanced fibrosis and cirrhosis," says Loomba, although he concedes that its high cost will make it less likely to be used widely. Performing MRI on very obese patients can also be problematic because specialized instruments that can accommodate larger bodies are required. However, MRE has been shown to be a promising tool in the context of clinical trials, particularly when combined with another MRI-based technique called proton density fat fractionation (PDFF), which accurately measures steatosis. Loomba and his colleagues were the first to demonstrate the power of this pairing[1], which they used to monitor the response of people with NASH to the drug ezetimibe, a potential treatment.

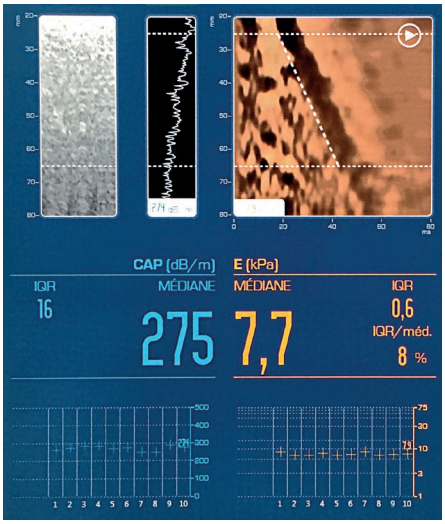
Even without directly observing the damage wreaked by fibrosis, clinicians can gain important insight by monitoring steatosis using PDFF or ultrasound-based methods. "Steatosis is the first thing that goes away if you start implementing lifestyle changes," says Vlad Ratziu, a hepatologist at Université Pierre et Marie Curie in Paris. That effect makes it valuable to measure the amount of liver fat and how it changes in response to interventions. Such monitoring could also aid in determining a prognosis, because it is the build-up of fat that fuels fibrosis in the liver. About 25 clinical studies have used MRE–PDFF to measure the response of fatty liver disease to treatment, Loomba says. "If you can say that you've reduced liver fat by 30% or 40%, that translates into improvement of NASH upon biopsy," he says.

MISSING MARKERS

For many diseases, a sample of blood can offer a helpful window on what is happening deeper in the body. But the current arsenal of blood tests for NAFLD has left clinicians wanting. "I don't use them a lot," says Lai. "When I looked at the data, I wasn't that convinced."

The most widely used metric for the blood-based monitoring of fibrosis is probably the NAFLD fibrosis score, which has been validated repeatedly in clinical testing and combines data on body mass index and blood-sugar and liver-enzyme levels. As with FibroScan, the NAFLD fibrosis score is best suited to revealing who is at lowest risk of developing the condition, with only 4% of cases of advanced fibrosis missed. The downside is that fibrosis is falsely detected in almost 50% of people tested. Clinicians have also designed and validated several blood tests, but none is ideal. "All of them have a diagnostic accuracy of 80% or less, and that's not something we can base a clinical decision on," says Loomba.

The biggest unmet need is a biological indicator (biomarker) that can be used to distinguish the mild fibrosis that is associated with steatosis from the more severe and aggressive fibrosis that contributes to NASH. A considerable obstacle to biomarker discovery is the nature of fatty liver disease, which has a long and complex progression that has proved difficult to untangle. "You need to identify these patients by liver biopsy, and then you need a follow-up over 10 or 20 or 30 years," says Castera. "These kinds of studies are difficult to perform." NASH is dynamic, driven both by internal physiological processes and by the lifestyle of each patient. The condition's tendency to advance or retreat unpredictably as people gain or lose weight makes it challenging to monitor, says Lai.



A FibroScan reading from a person with suspected non-alcoholic fatty liver disease.

An influx of drug candidates for treating NASH is spurring further interest in the development of blood tests that could eventually spare drug-trial participants from several rounds of biopsy. For example, biopharmaceutical company Genfit, located near Lille in France, has been using studies of the drug elafibranor as an opportunity to devise and assess diagnostic tests that measure the levels of proteins and small gene-regulating molecules known as microRNAs found in blood that indicate the presence of active disease. Ratziu also sees potential in blood tests being developed by Nordic Bioscience in Herlev, Denmark, and Bristol-Myers Squibb of New York that detect products of the synthesis or degradation of collagen, a structural protein with a central role in fibrosis. "Right now, you can tell the stage of fibrosis you are in, but that doesn't tell you how hard the engine is running," he says. "There are some interesting and promising indicators coming from the measurements of these by-products." He also points to multinational efforts that focus specifically on the blood-serum biomarker problem, including a European project called LITMUS that is being overseen by the Innovative Medicines Initiative, a public–private partnership based in Brussels.

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Although clinicians are used to turning to blood for answers, other products of the body could also provide useful diagnostic clues. Loomba has collaborated with the J. Craig Venter Institute in La Jolla, California, to demonstrate that faeces could offer an insight into fatty liver disease (see page S94). The team conducted a survey of the genomes of gut bacteria from 86 people with NAFLD and either mild or severe fibrosis, as determined by liver biopsy[2]. The results revealed clear and measurable differences between the populations of microbes that were associated with early-stage or advanced disease, and with greater diagnostic power than most existing blood tests. "We were surprised by the accuracy we got," says Loomba. "We verified it in an independent cohort of patients with cirrhosis and controls, and now we're doing validation studies."

CROWD CONTROL

Even if none of these diagnostic tools is ready to supplant the biopsy, a combination of both approaches can help clinicians to comb through the large numbers of individuals who are at risk of developing NAFLD — especially given that the main risk factors are well established. "If you're diabetic, you're 50 or older, and you're obese, you need to be screened," says Loomba.

But some clinicians see the need for more-aggressive surveillance. In November last year, Castera and his colleagues issued a call to screen the general population[3]. "You can start with biomarkers, because it's easy to do blood tests in a large population and you can get rid of most people who are not at risk," he says. "Then you can perform transient elastography and, at the end, biopsy." Castera cites screening studies indicating that 5.6–7.5% of the public may harbour liver fibrosis without realizing it — and that 0.6–0.7% of those people will already show signs of cirrhosis[3]. He says that many general practitioners and even specialists in obesity and diabetes may not realize that their patients are at risk of severe liver damage.

Building an awareness of liver health is a motivating factor for Loomba, who notes that there are other important predisposing factors for NASH that are only now becoming clear — such as having an immediate family member with NAFLD-related cirrhosis, which can increase the risk by up to twelvefold[4]. "I don't want to wait for people to die from cirrhosis or develop liver cancer, but rather start acting now to detect something," he says. "We may not have a perfect biomarker yet, but vigilance is very important." ■

Michael Eisenstein *is a freelance science writer in Philadelphia, Pennsylvania.*

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