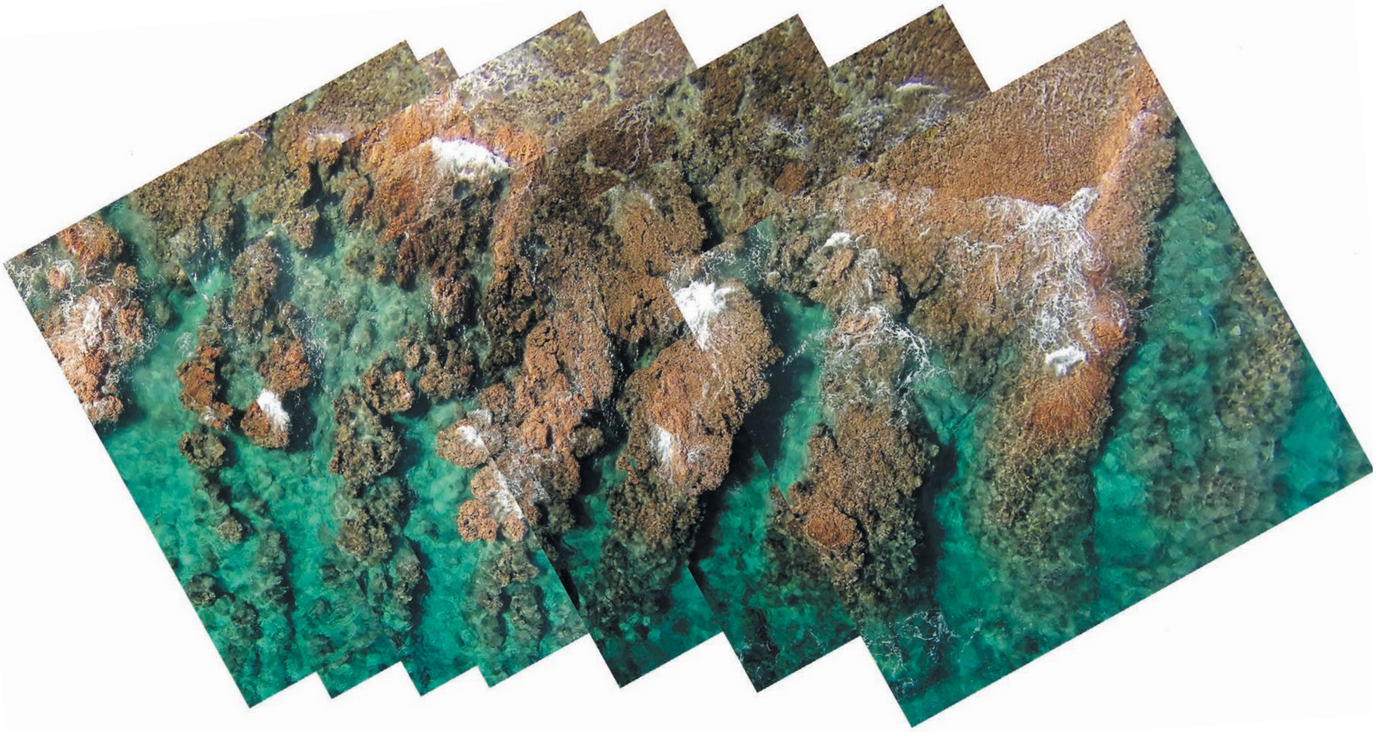
TECHNOLOGY FEATURE

POCKET LABORATORIES

Mobile phones are helping to take conventional laboratory-based science into the field, the classroom and the clinic.

E. REYNAUD/N. LE BESCOT/J. GIRARDOT/UCD/VA'A MOTU/EXPLORE



Researchers got these images of the French Polynesian coastline by flying a smartphone on an ultra-stable 'Cody' kite.

BY JEFFREY M. PERKEL

As spring turns to summer along the east coast of the United States, thoughts turn to holidays, beaches, picnics — and mosquitoes. Prince William County, Virginia, southwest of Washington DC, is no exception. In 2016, county officials set traps to collect and test mosquitoes for the presence of disease-causing viruses. Usually, the testing involves taking the insects back to the lab and analysing them for signs of the pathogens' nucleic acids — a process that can take days. But last September, Joseph Russell was able to get those same data from the air-conditioned comfort of his car — all thanks to his smartphone and a handheld instrument known as the two3, made by Biomeme of Philadelphia, Pennsylvania.

About the size of a small laptop speaker and controlled by a plugged-in iPhone, the two3 can test each of three nucleic-acid extracts for two sequence targets at a time. Simply pop open the top, add sample tubes and press start. "It was phenomenal," enthuses Russell, a postdoc at MRIGlobal in Gaithersburg, Maryland, who ran the device from his car's cup-holder as he drove from site to site. "By the time I had collected the next round of mosquitoes, I knew the results from the previous spot."

Russell's experience illustrates the ease with which researchers are migrating their science from the lab into the field, thanks to an increasingly powerful and enabling tool that many people already carry in their pockets — the smartphone.

Combining a computer, camera, Global Positioning System, networking, sensors and batteries in one compact package, smartphones are like "a Swiss army knife" that can be used almost anywhere, says Aydogan Ozcan, an electrical and biological engineer at the University of California, Los Angeles. Ozcan has spent the past decade fashioning apps and hardware that turn the phones into ever-more-powerful microscopes and biosensors.

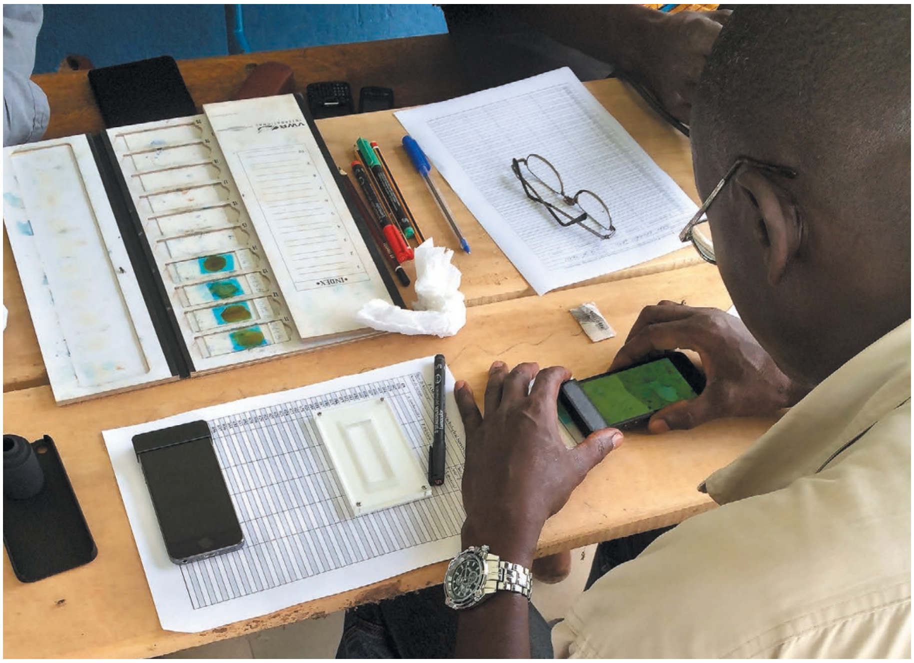
And with billions of devices in circulation and cellular networks that are constantly improving in terms of coverage and data-transmission speed, researchers are using the phones to take their science ever-farther afield.

But powerful as they are, smartphones were initially made with the consumer market in mind, not science. In their quest to gain customers, manufacturers continually push the envelope of what their phones can do, especially in terms of camera quality. "How many consumers 'need' that 40-megapixel camera? Maybe a fraction," Ozcan says. But, he adds, scientists can capitalize on the improving image sensors and the advantages that those bring. ▶

Often, researchers can gain those benefits right out of the box, no custom apps required. Matthew Dietz, an orthopaedic surgeon at the West Virginia University School of Medicine in Morgantown, devised a method to use the iPhone's accelerometer — the built-in sensor that allows users to control video games by tilting their screens — to measure the range of motion of a limb joint. His colleagues' reaction was mostly one of surprise, Dietz says: "I didn't know my phone could do that!"

Today, smartphones are used for a wide range of scientific and medical purposes. Ozcan's group has exploited the technology to design successively more sophisticated and sensitive imagers, including ones that can visualize individual viruses and DNA molecules. Mechanical engineer David Erickson and nutrition scientist Saurabh Mehta, both at Cornell University in Ithaca, New York, have developed an iPhone-based system called the NutriPhone that can test for 'micronutrients' such as vitamin B_{12} and iron in patients' blood. Originally, users placed a test strip into an accessory placed in front of the phone camera. But Erickson has now developed a wireless version that minimizes contact between bodily samples and the phone. "If you're performing a diagnostic, particularly for a number of people, on your own mobile phone, there's a possibility of contamination from the sample to the phone, and then you're putting it up to your ear and then, who knows what [can happen]?" he says. Erickson founded a company, VitaScan in Ithaca, to commercialize the technology.

There are even smartphone-based DNA sequencers. In the United Kingdom, Oxford Nanopore Technologies has announced a commercial device called SmidgION, which the company anticipates will be ready by the end of 2017. And in January, Mats Nilsson of Stockholm University, working with Ozcan, demonstrated a 3D-printed smartphone attachment to detect DNA mutations in sections of tissue. The team used the device (with a Nokia Lumia 1020 Windows phone) to count cancerous cells using fluorescence techniques, and Nilsson hopes it will ultimately enable rapid diagnosis of antibiotic-resistant tuberculosis in India — a condition that all too frequently takes months to detect in that part of the world.



ISAAC BOGOCH

The CellScope microscope smartphone attachment allows technicians to examine samples for the presence of parasites while at their desks.

DEMOCRATIZING DIAGNOSTICS

Perhaps nowhere is the game-changing potential of smartphones more obvious than in developing countries. In 'resource-poor' environments, trained personnel tend to be scarce and laboratory equipment even more so. Key infrastructure, such as electricity and clean running water, are often unreliable. Cellular networks, however, offer some resilience.

In 2014, Isaac Bogoch, a tropical-medicine specialist at the Toronto General Hospital Research Institute in Canada, spent time in the rural town of Grand Moutcho in the south of Côte d'Ivoire, looking for evidence of the parasitic infection called schistosomiasis, which can cause liver, gastrointestinal and urogenital complications.

Schistosomiasis is endemic in Côte d'Ivoire, Bogoch says. Spread by contact with contaminated water, the disease is easy to diagnose and easy to treat — assuming health-care workers have access to a microscope and are trained in how to use it. All too often, they don't.

To close that gap, Bogoch and his colleagues turned smartphones into portable microscopes and taught local technicians how to use them to test urine and faeces from potential patients. "Rather than transferring people or specimens to laboratories that are far away, we can bring the lab to the people," he says. Such strategies are democratizing health care, Bogoch notes. But they also facilitate epidemiological surveillance, and open the door to remote or even automated image analysis. For instance, Johan Lundin, research director at the Institute for Molecular Medicine Finland at the University of Helsinki, has developed an automated fluorescent slide scanner using mobile-phone components, which he recently tested in Tanzania, also looking for schistosome infection. Although the school at which the trial was conducted had no electricity, Lundin says, slide images collected in the field could be uploaded to servers in Helsinki at the rate of 20 fields of view per second through the cellular network. They could then be downloaded back in Tanzania for immediate assessment. Lundin has also formed a company, Fimmic, to commercialize automated pathology slide analysis in the cloud.

Bogoch's team trained local microscopists to identify schistosome eggs in human urine and faeces while located in more-rustic environs. Rather than working in the usual laboratory setting, they would do their analysis from "a picnic table outside of a clinic in a field".

The test used a simple 3D-printed mobile-phone attachment called CellScope Schisto, developed in the lab of Daniel Fletcher, a bioengineer at the University of California, Berkeley. The CellScope is basically a snap-on case that positions an inverted mobile-phone lens over a smartphone's existing camera to magnify the image. The team also tested a commercial handheld microscope called the Newton Nm1, and compared the findings to those taken using a conventional clinical microscope. Both handheld devices were sensitive to low levels of infection, but the Nm1 performed better, probably because the CellScope has no built-in slide-scanning functions, Bogoch says; the team is now addressing that limitation (J. T. Coulibaly *et al. PLoS Negl. Trop. Dis.* **10,** e0004768; 2016).

Meanwhile, Fletcher's team has used the CellScope to look for evidence of another parasite, the filarial nematode *Loa loa*, in Cameroon.

To do so, Fletcher's team supplemented the CellScope's inverted lens with an array of light-emitting diodes (LEDs), an Arduino (devices that make use of the low-cost minicomputers increasingly being used by researchers to collect and analyse data), Bluetooth and an automated sample translation stage, all of which were controlled by an attached phone. To run the test, the researchers, working with partners in France, Cameroon and the US National Institutes of Health, put a droplet of unprocessed patient blood into a capillary, load that capillary into the iPhone attachment, and then capture short 5-second movies of the capillary one field of view at a time. In this way, they can look for disturbances in the distribution of red blood cells that would indicate the presence of a wiggling *L. loa* worm. Images are analysed on the phone itself, with total time from finger prick to diagnosis of about 3 minutes.

The device gives comparable results to conventional blood-smear analysis, with no false negatives and only two false positives in the 33 samples (M. V. D'Ambrosio *et al. Sci. Transl. Med.* **7,** 286re4; 2015); Fletcher says that it has since been validated in hundreds of people and used to test thousands of people with river blindness, which is caused by the *Onchocerca volvulus* worm. "Making a device in the lab, as academics like to do, and showing that it can work, is one thing," he says. "But actually making devices that work reliably in the field is a very stressful transition — but one that's incredibly satisfying when it does indeed work."

WIDER APPLICATIONS

Others use their smartphones for pedagogical purposes. University of Pennsylvania bioengineering graduate students Megan Sperry and Heidi Norton worked with Biomeme and the educational group TechGirlz to introduce 18 schoolgirls to modern molecular biology using the iPhone.

The team ordered fresh sashimi from three Philadelphia restaurants and tested the fish using the two3 to see whether the menu accurately described what species was served. In about half the cases, it didn't.

For students, Sperry says, being able to "connect the dots" between the classroom and real life made the exercise particularly interesting. "It was the perfect experiment as a first exposure to lab experience," she says. "There's a real-world example: there's fish, we're genotyping it, we're going to see if it's the correct fish or not."

Others have used their phones to build instructional microscopes. Bioengineer Ingmar Riedel-Kruse at Stanford University in California, for instance, developed a 3D-printed LudusScope. The device includes a joystick-controlled LED array that students can use to drive light-responsive single-celled protozoa around the field of view. And Julien Colombelli, an engineer and manager of the Advanced Digital Microscopy Core Facility at the Institute for Research in Biomedicine in Barcelona, Spain, has combined the power of smartphones and LEGO to illustrate the principles behind light-sheet microscopy.

The 'LEGOLish' system is not a true microscope, Colombelli says — it contains no magnification lenses. But it can image objects measuring 1–2 centimetres, about the size of a mouse embryo.

The system passes light from a cheap laser diode through a water-filled tube, which acts as a cylindrical lens to create a thin sheet of light. A series of LEGO gears translates and rotates the sample through that light sheet to produce optical sections, which are then captured on the phone. The set-up costs around US$200, not including the phone.

Colombelli and his colleague Jordi Andilla at the Institute of Photonics Sciences, also in Barcelona, first designed the LEGOLish to be used as prizes for the best posters at a light-sheet microscopy conference they organized in 2014. But they have since upgraded the design to make it suitable for scientific applications, albeit at ten times the cost. Researchers could use that modified design, which is built on top of a stereomicroscope, to perfect their sample preparation procedures before reserving time on a core facility's instrument, he says. "We believe this would help a lot of labs, because they would have easy access, for less than $2,000, to a system that they can use and build in a week's time."

FROM LAB TO FIELD

Their portability makes smartphones particularly useful in remote locales. Late last year, for example, Peter Countway, a marine microbiologist at the Bigelow Laboratory for Ocean Sciences in East Boothbay, Maine, took the Biomeme two3 to Palmer Station in northern Antarctica. He and his team used the device to study how ocean bacteria metabolize dimethylsulfoniopropionate, an organic sulfur compound produced by phytoplankton that has been implicated in global weather patterns.

And Emmanuel Reynaud at University College Dublin has taken his smartphone to the tiny coral atoll of Fakarava in French Polynesia to study the health and structure of coral reefs across a series of length scales. To get the widest-angle view, his team blends twenty-first-century technology with a Cody kite, an ultra-stable design developed by plane pioneer Samuel Franklin Cody in 1901.

"Rather than transferring people or specimens to laboratories that are far away, we can bring the lab to the people."

The team used the kite to loft a cheap Android phone into the air, then dragged the kite behind a kayak for about six hours. The phone takes a picture every 20 minutes, then compresses the image and beams the data to a computer down below. The images are later processed to map the reef in 3D. The total cost for the hardware is about $400 — cheap enough that they can leave it behind for local researchers to continue the surveillance once the team has returned to Dublin.

After all, says Reynaud, even in Fakarava, which has a population of just 400, phones are everywhere. "You're just showing them that, instead of texting all day, you can also do useful things."

AND TO THE CLINIC

Increasingly, smartphones (and related, wearable devices such as the Apple Watch, Fitbit, and Alphabet's newly announced Study Watch) can collect medically relevant data, such as step-counts and heart rate. In April, the US business news outlet CNBC reported that Apple was developing sensors to measure blood sugar through the skin. Researchers are finding new ways to use such data to answer scientific questions.

Apple's ResearchKit, for instance, allows scientists to use iPhones to recruit people into and conduct clinical studies. "I thought it was a pretty brilliant idea," says Yvonne Chan, director of Personalized Medicine and Digital Health at the Institute of Genomics and Multiscale Biology at the Icahn School of Medicine at Mount Sinai in New York City. Many users take their smartphones everywhere they go, she says; she confesses to being "a smartphone addict — it literally is on me 24/7". And ResearchKit provides a way to marry that universal appeal with people's innate scientific curiosity, to do something "really awesome", she notes.

When Apple launched ResearchKit in 2015, it announced five preliminary studies that make use of the software. Some studies leverage smartphone sensors to document patient symptoms; others used them to survey patients or to collect data that are input by the phone users. Chan was principal investigator on one such study, the Asthma Health study, which asked participants to answer questions about their health each day, then correlated that information with where the people had been. Thanks to Apple's marketing savvy, she says, uptake of the app wildly exceeded her expectations, with some 35,000 downloads and 3,000 participants fully enrolled and consented in just three days.

Ultimately, however, the ResearchKit model may allow smartphone-based studies to move beyond observation to provide truly personalized health care. Jennifer Radin, an epidemiologist at the Scripps Translational Science Institute in La Jolla, California, is a member of a team that just released a ResearchKit-enabled app that will survey pregnant women about their symptoms. By tapping into a large and diverse subject pool, she says, the team hopes to use the data to offer personalized recommendations that are tailored to a person's body type or ethnicity, to identify complications earlier and even reduce to the number of visits to the doctor.

Whether such benefits ever come to pass, one thing is certain: the global game of technical one-upsmanship between smartphone developers shows little sign of slowing. That's good news for consumers. And it's great news for science. ■

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