Improving healthcare, particularly in the developing world, will require low-cost diagnostic devices that can be used quickly and easily to meet the needs of people living in remote locations that often lack doctors, clean water, and electricity. These diagnostic tools need to be rugged and reliable, inexpensive, and insensitive to changes in temperature and humidity. Ideally, they should run without electricity and fit easily in a backpack that an aid worker could carry on foot or by bicycle.

With its ability to miniaturize sample analysis from milliliters to microliters, all within an area of a few square centimeters, microfluidics has the functional capabilities to fulfill this task. Since the 1990s, the Defense Advanced Research Projects Agency (DARPA) has invested in microfluidics for advancing portable devices on the battlefield. “The difference between what the military needs to do in taking care of soldiers and [what is needed for] global health is actually very, very small,” says Paul Yager, professor of bioengineering at the University of Washington in Seattle.

Although a microfluidic chip drastically reduces both sample and reagent volumes used in laboratories, the devices produced and used in laboratory settings won’t work in the developing world. They still require clean water, fluid pumps, and expensive detectors—along with electricity to power these components. Over the last decade, researchers have searched for ways to overcome these technical and manufacturing challenges. Some efforts have scaled down chip analysis into streamlined battery-powered devices with disposable microfluidic cards. But even those devices may prove too costly. Now, a new low-cost solution has emerged from an über-simple concept: devices made from paper and tape.

**Shuffling cards**

In the late 1990s, the development of soft lithography methods using polydimethylsiloxane (PDMS) by George Whitesides’ group at Harvard University and others brought microfluidics out of the clean room and into the mainstream academic laboratory. Researchers could design and fabricate devices with channels by building layer upon layer of soft plastic. To run, such systems rely on complex networks of pumps and valves with microscopes or fluorescence to detect signals. “Even if [those things] work in a portable setting, they might not be very cheap,” says Samuel Sia of Columbia University.

While a postdoc in the Whitesides group at Harvard, Sia was intrigued by the challenge of rethinking and streamlining microfluidic devices. He and his colleagues looked for ways to put reagents on a disposable plastic card and develop a small portable device that would run it. The big manufacturing challenge was finding a way to produce the microfluidic cards cheaply using molded plastic. He and his colleagues tweaked the parameters used for injection molding, the process used to mass produce plastic objects such as pens. Such processes had generally only been used to make features on the order of millimeters, but Sia and his colleagues found ways to produce micron-sized features. Sia is one of the founders of Claros Diagnostics, which has been developing this handheld system. They have already designed cards for a developed-world application: a quick test for measuring prostate-specific antigen (PSA) as a doctor’s office–based screening tool for prostate
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The paper chase

Even with developments to make plastic microfluidics simpler and less expensive, many researchers aren’t convinced that these devices can operate both cheaply and consistently enough for widespread use throughout the developing world. “The promise of microfluidics is still there,” says Bernhard Weigl, the principal investigator of PATH’s Center for Point-of-Care Diagnostics group for global health. “The problem is that the technology to do it isn’t trivial.”

Several years ago, Whitesides and his colleagues decided that they couldn’t reach developing world targets by simplifying traditional plastic microfluidic systems. “What we did was to start with the least expensive thing that we could think of and see if we could add capability,” Whitesides says. Inspired by the idea that paper and printing could give them the patterns to do chemical analyses, they replaced plastics and injection molding with hydrophobic lines made from photoresist or wax printed on paper. So, instead of relying on pumps, the water moves through paper via capillary wicking. They also try to use colorimetric assays and couple those with cell phones, Whitesides adds, “because in the developing world, doctors are even scarcer than money.”

Paper also offers ways to siphon a single droplet into many wells, a feat that’s much more difficult to accomplish in plastic. By stacking patterned sheets with holes and attaching them with double-sided tape, 3-D structures emerge that allow sample fluid to wick between layers; up to 64 test wells can be created in a device the thickness of old shirt cardboard. Other printing strategies could create electrodes on paper for inexpensive optical detection. The Claros Diagnostics system uses gold nanoparticles bound to IgG which in turn bind to an agent of interest. They then develop those spots using silver to amplify the signal up to a million-fold for inexpensive optical detection.

An important innovation in such systems is the implementation of a simple optical readout that avoids detection schemes requiring fluorescence and additional equipment. The Claros Diagnostics system uses gold nanoparticles bound to IgG which in turn bind to an agent of interest. They then develop those spots using silver to amplify the signal up to a million-fold for inexpensive optical detection.

Another collaboration based at the University of Washington has followed a similar approach. Since 2005, researchers there, along with those from the Seattle-based non-profit PATH and two for-profit companies—Micronics and Nanogen (now part of the ELITech Group)—have been developing a proof-of-concept device through the DxBBox project, supported by the Bill and Melinda Gates Foundation. Yager and his colleagues were trying to take an idea that they’d developed—pushing liquids around on disposable polylaminate cards under the control of a base station—and make it as accessible and inexpensive as possible. The device has the capability of doing both immunoassays and nucleic acid-based assays to test for a variety of infectious diseases characterized by fever: malaria, typhoid, influenza, rickettsia, measles, and dengue fever.
used to send results for a more detailed analysis.

Yager and his colleagues at both the University of Washington and PATH are moving into paper microfluidics as well; the DxBox already used nitrocellulose components within its card. After watching a late-night infomercial in 2008 about a paper cutter for craft projects that would cut paper in particular shapes, Yager realized that he could use the same principle to shape nitrocellulose channels for use in a low-cost microfluidic device. His team recently received a two-year $1 million NIH Challenge grant to develop the idea: their credit-card-sized prototype integrates a nitrocellulose channel cut in particular shapes within pieces of injection-molded plastic. The plastic then sits within a water-filled trough. The nitrocellulose is patterned with reagents, and the shape of the channels controls when those reagents are delivered to the final detection point. Each device could be made for about $1, Yager says.

Challenges in commercialization

Even as academic researchers, non-profits, and small companies develop new ideas for microfluidic devices, commercialization is an important piece of the puzzle. Although these initial technology developments are happening with public research funding, donations, and grants from non-profits such as the Gates Foundation, there’s not a financial incentive for a company to commercialize a product that will be sold at cost or even given away. “Where that transition happens from grants and donations to a self-sustaining financial enterprise,” Sia says, “[is] something, I think, that people have to think more carefully about.”

“When doing a startup, [venture capitalists] always want to exit before you get to the developing world,” says Ryan, who was formerly the president and CEO of AVANT Immunotherapeutics and has worked on both for-profit and non-profit vaccine development. For-profit companies are interested in licensing DFA’s technology, which Ryan sees as an important component to their overall success. To harness that revenue, DFA has set up a for-profit subsidiary, Paper Diagnostics, whose revenue will help sustain the work of DFA on projects for the developing world.

“It’s difficult to get the technology simple enough,” Ryan says. Much of technology innovation in the United States is focused on making devices cleverer and more complicated—and therefore more expensive and more difficult to regulate, she adds. “The whole point here was to go back to something as simple as printed paper and comic books.”

Written By Sarah A. Webb, Ph.D.