

Lab on a Stamp: Paper-Based Diagnostic Tools

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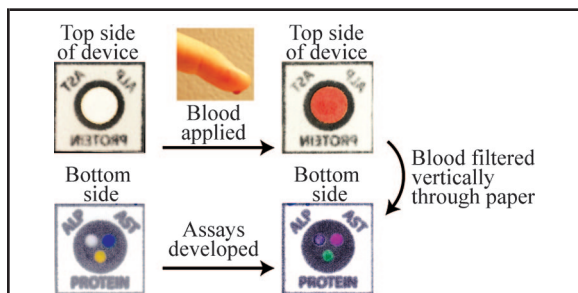


Fig. 1. A low-cost, micropatterned, paper-based device the size of a postage stamp was designed to use blood from a fingerstick to measure 3 markers of liver function.

The device enables quantitative analysis of alkaline phosphatase (ALP), aspartate aminotransferase (AST) and total protein markers within 35 min. Reproduced with permission from Vella et al. (1).

About 2 decades ago, with the invention of the i-STAT® System (Abbott Laboratories), clinical laboratories began moving blood and serum through microchannels for efficient point-of-care diagnostics. To produce the most precise microchannels, valves, and chambers $\leq 100 \mu\text{m}$ wide, researchers turned to silicon. But silicon is expensive, and throughout the last decade, scientists have searched for other materials that could be put to use. Although many have claimed that their inventions could serve as cheaper, simpler diagnostic tools, few have pushed the potential of these new technologies to serve the developing world, where low-cost, simple-to-use diagnostic tools can be game-changing. Enter George M. Whitesides, a professor of chemistry at Harvard University who specializes in “labs-on-chips.” Dr. Whitesides and his laboratory have created micropatterned, paper-based analytical devices (μPADs), a paper microfluidics tool the size of a postage stamp (Fig. 1). The technology is currently being licensed for development to Dr. Whitesides’

nonprofit company, Diagnostics for All. *Clinical Chemistry* chatted with Dr. Whitesides about his tool, as well as with Dr. Peter Wilding, a professor emeritus of laboratory and pathology at the University of Pennsylvania (who published one of the first reports on microfluidics in this journal).

Why Is This Invention Important?

The paper microchip is a first-of-its-kind vertical-flow diagnostic tool composed of paper, wax, and a filter. Whitesides began thinking about a new technology for the developing world when he was working for the military on a device that would detect biohazards in the field. He wondered if a similar type of tool—fast, point of care, simple—could be created for use in developing countries. When designing products for the developing



world, “people typically start with ‘what we do in the developed world’ and then cut the cost,” said Whitesides. “We went the other way by asking, ‘What is the simplest way that can have biological implications?’”

The challenge was to create a tool that could be used for diagnosis in resource-deprived settings—such as those lacking electricity, proper disposal methods, or public health infrastructures—and to do so cheaply. Silicon was too expensive. The idea of using paper dawned on Whitesides when he realized that print materials, such as comic books, were distributed all over the world, which meant that paper and ink were almost universally avail-



able. The idea took hold, and from it came the first-generation μPADs . With this paper-based microchip,

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wicking replaces electricity as a way to move liquid, the chip can be incinerated for disposal, and the colorimetric system can be interpreted by untrained individuals. Paper-based microchips that analyze liver function have been distributed to India and will be distributed in the coming months to Vietnam, at an estimated cost of \$0.05 per chip. The team has also moved beyond the original concept toward the development of μ PADs that work in commercial electrochemical readers, such as glucometers, and paper-based ELISAs.

How Does It Work?

The device works by wicking blood or urine toward separate zones that contain assay reagents. The device is produced by printing microchips of patterned paper (17 mm²) onto sheets of chromatography paper with a Xerox color printer. One sheet of paper can be printed with 150 devices, an astounding number. In contrast to the color inks and toner of typical printers, this souped-up printer squirts out wax ink: For μ PADs designed for use with over-the-counter glucometers, the microfluidic electrodes are printed with silver ink, and the electrical interconnects are printed with graphite. This process creates hydrophobic zones and channels on the hydrophilic paper. At the “end” of the channels are 3-mm circles that contain manually dotted assay reagents. A 15- μ L urine sample or blood sample obtained via a finger prick with a disposable needle can be dotted onto the square. Then, capillary wicking pulls the sample along the channels to the reagent zone. With blood samples, erythrocytes are separated from plasma with an embedded filter membrane. According to the Whitesides team, the colorimetric assays generally finish in about 30 min. The assay chip either can be analyzed on site with the aid of an on-chip color chart or can be photographed with a cell phone and the image sent to a central location for assessment by a trained professional. For the electrochemical μ PAD technology, the paper microchip inserts directly into an over-the-counter glucometer. An aqueous solution of analytes then is applied, and the glucometer presents the results on its screen.

Where Can This Technology Fit in the Clinical Laboratory?

Whitesides has big visions for his tiny paper chip. He hopes it one day will be a critical tool in both developed and developing countries for diagnosing fevers of unknown origin, tuberculosis, diabetes, and anemia, among other diseases. Whitesides is also using grant monies to create paper tests for applications

outside of public health, including agriculture, for which he is currently developing a diverse set of tests, including, for example, a test to help owners of small farms identify aflatoxin on crops and a pregnancy test for cows.

As Dr. Whitesides moves ahead, tweaks will be made along the way. For example, this microchip may actually be too small. “You can’t actually hold a postage stamp,” points out Whitesides, suggesting that perhaps μ PADs 2.0 should have a nonfunctional handle.

Dr. Peter Wilding, the microfluidics expert at the University of Pennsylvania, believes the shelf life of the disposable diagnostics tool must be rigorously tested. Whitesides agrees. In one of the Harvard team’s studies of measuring liver function markers with a blood sample, the investigators found that the test for one of the markers, alkaline phosphatase, worked as expected after a shelf life of 3 months at room temperature, whereas the aspartate aminotransferase test showed discoloration after storage under these conditions. The Harvard team writes that “viable devices must still function after storage in different environments for at least 1 year. . . . Extensive testing in different environments (cool and hot, dry, and humid) would be required to determine the shelf life of these devices.” Whitesides says that one of his priorities is to stabilize the biological aspects of his tests without the need of a refrigerator.

Wilding is also interested to see whether and how production of the test, now manufactured manually, could be automated, but his most pressing question is how the paper-based microchip will be incorporated into point-of-care systems used around the world today, much as traditional blood glucose monitors snap into digital systems. Despite his questions, however, Wilding is nothing short of admiring, describing Whitesides’ work as “phenomenal,” and is eager to see what the future holds for μ PADs. “It’s the basis of a great device,” Wilding concludes. As to the larger question of how μ PADs will be incorporated into the larger point-of-care diagnostics systems, he says that the path of uncertain futures is “just how new technologies go.”

On his end, Whitesides says Diagnostics For All will optimize the technology, thereby taking its shelf life, manufacturing, and clinical trials to “the next stage.” He is committed to continuing the development of the technology in his laboratories, with the hope that this paper-based tool he has imagined for the developing world will some day be used in the developed world. “I think we have a good technological idea,” he says.

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Reference

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