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Opinion

Medicine Unplugged: The Future of Laboratory Medicine

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We live amidst a digital revolution occurring in mobile healthcare. The remarkable and explosive progress in wireless medical devices has been catalyzed by the software of apps and the hardware of "adds." Wireless diagnostics tools such as the AliveCor smartphone-enabled electrocardiograph, the vScan pocket ultrasound, and the CellScope smartphone-based otoscope are poised to deliver diagnostic information faster, cheaper, and at the point-of-care (POC).[4] Leveraging the power of >6 billion active cell phones, a number far greater than the number of toothbrushes or toilets in the world, these devices can be used anywhere there is a mobile signal, thereby achieving a "flattening" of the Earth with respect to access to mobile-health technologies *(1)*. Now, the convergence of smartphones and innovative biosensors based on microfluidics and microelectronics is tackling the next big challenge for wireless health: portable biochemical analysis in the form of a handheld lab-on-a-chip (LOC). Capable of accommodating a wide range of testing modalities—from analytical chemistry to microscopy to POC genomics—LOC systems represent a new model for laboratory medicine, in which a smartphone-enabled portable laboratory is brought to the patient instead of the patient being brought to the laboratory. We examine recent advancements in mobile diagnostics enabled by microfluidics and LOC technologies for POC clinical testing.

Data and Diagnostics

Vinod Khosla, the prominent venture capitalist, recently opined that in the future a combination of innovative algorithms and next-generation diagnostic devices could replace 80% of doctors *(2)*. This radical prediction reflects the fact that the current wireless health ecosystem is home to a growing network of distributed health data procured by an array of diagnostic devices. Aggregation and algorithmic processing of the data will ultimately be necessary to create artificial-intelligence and decision support for patients and the medical community. Consequently, there is enormous interest and investment in wireless diagnostics, as exemplified by the $10 million Qualcomm TriCorder X Prize. Announced in 2012, this landmark competition aims—in the spirit of the iconic medical scanner used on the *Star Trek* television series—to award the development of a noninvasive wireless device capable of accurately diagnosing 15 different conditions.

Microfluidics and LOC

The TriCorder X Prize does not mandate the inclusion of any particular mobile-health technology, but given the central role of biochemical testing in medical diagnostics, data obtained by wireless LOC systems will undoubtedly assume a prominent role in any winning solution. Able to serve as portable platforms that house such technologies as microfluidics, LOC systems are designed to provide POC information, such as results for analytical chemistry, immunoassays, and flow cytometry. Specialized for a single laboratory modality, single-chip systems can be cost-effective to produce and operate. By combining several laboratory modalities and more complex analytical techniques, multiplexed LOC devices—also known as "micro total analysis systems"—can serve as complete mobile laboratories *(3)*.

Microfluidics and microelectronics form the foundation for LOC engineering. Microfluidics devices use a combination of intricate fluid channels and microelectronics components, such as nano- and microscale fluid wells, valves, actuators, nanowires, and pumps, to quantify molecular interactions within small sample volumes (<10 nL). By using a customizable array of sensors, reagents, and substrates, microfluidics devices serve as miniature factories that "shrink the plumbing" typically found in traditional laboratories into a palm-size device. The advantages are substantial: speed, portability, and capability to perform a wide array of biochemical testing, including immunoassays, molecular analysis, blood chemistries, and flow cytometry *(4)*.

Integration with smartphones will ultimately help emerging LOC devices bridge the existing gap between bioengineering prototypes and commercially viable clinical tools. By providing mobile access to computing power and Internet connectivity, smartphones also offer sensors, cameras, and high-resolution displays that

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[4] Nonstandard abbreviations: POC, point-of-care; LOC, lab-on-a-chip.

can be used to visualize data and enable telemedicine applications. The SmartBioPhone, a POC platform for genomic analysis and infectious-disease testing, represents one example of integration between a smartphone and LOC systems *(5)*.

Clinical Applications for LOC

Over-the-counter glucometers are important tools for managing diabetes, but they require frequent fingersticks for blood sampling and have a suboptimal accuracy of measurement, typically 15%–20% *(6)*. A recently introduced glucometer, the iBGStar (Sanofi), is tightly integrated with the Apple iPhone to display, graph, and archive glucose measurements. Telcare's glucometer goes one step further by replacing external phone connectivity with a built-in cellular chip capable of sending results to an online portal immediately after measurement. Through the use of a tiny 26-gauge needle that can be inserted into subcutaneous tissue for glucose sampling, a continuous glucose monitor represents a minimally invasive, microfluidics-based biosensor that can wirelessly communicate glucose measurements to a portable receiver and directly to a smartphone.

In addition to highly specialized LOCs such as blood glucometers, the incorporation of additional elements, such as optical sensors, nanowires, and specialized reagents allows LOCs to perform complex immunoassays and electrochemistry tests to obtain data for basic metabolic panels, urinalysis, hormone concentrations in blood, and cardiac biomarkers. Disposable and portable, these LOCs could easily be used at home by patients on diuretic therapy to monitor electrolytes and by patients with chronic kidney disease to monitor serum creatinine, blood urea nitrogen, and quantitative asessments of urine protein. A POC LOC system from Alere is available for home measurement of brain natriuretic peptide in patients with congestive heart failure. This device aims to help guide outpatient management and to reduce the almost 25% 30-day readmission rate for patients with this costly, and prevalent, chronic disease. Integrating smartphones into the user experience for these LOC systems could provide patients with a familiar, manageable platform to analyze, visualize, and upload biochemical data from home. Low-cost paper-based systems that leverage colorimetric assays and smartphone cameras have even been used to bring advanced POC testing, such as analysis of liver function, to remote and underserved areas *(7)*. This timely access to biomarker information will allow patients to reduce their use of healthcare resources and manage chronic disease proactively.

Although outpatient POC coagulation testing is already available for checking the international normalized ratio for patients on warfarin therapy, LOC systems can use emerging microfluidics and microelectronics technologies to bring more complex analyses, such as flow cytometry and cell counting, to the home. Additionally, successful optical analysis of blood has also been demonstrated by adapting the onboard cameras in smartphones for POC microscopy outside the traditional laboratory environment. Combining smartphone microscopy and traditional microfluidics-based flow cytometry has allowed a broad range of hematologic information—from complete blood counts, detection of blood-borne pathogens, and characterization of specific cell types such as $CD4^{+}$ white blood cells—to be obtained at the bedside. Smartphone-enabled microscopy, image processing, and cell characterization with LOC systems can be readily applied in resource-poor areas for patients with HIV, hematologic malignancy, and anemia *(8)*.

In addition to the use of digital cameras for cell imaging, POC testing for infectious disease has already been demonstrated with LOCs that offer rapid diagnosis of HIV, malaria, tuberculosis, hepatitis, schistosomiasis, and Dengue *(9)*. These analyses can be performed by LOC genomics, proteomics, and immunoassays, such as those used in the GreeneChip and the stand-alone, self-powered integrated microfluidic blood-analysis system (SIMBAS). Deployment of LOC testing for infectious disease is critical in resource-limited areas, where rapid diagnosis and initiation of treatment could help prevent sepsis, prevent epidemics, and promote the efficient use of constrained antimicrobial resources. We envision the rapid sequencing of a pathogen's genome in minutes, soon after initial evaluation of a patient, rather than having to wait days for the results of cultures and sensitivities to be determined. With almost no sample preparation, the feasibility of single-molecule sequencing via a handheld device has already been demonstrated *(10)*.

POC genomics has the potential to radically improve pharmacologic management by rapidly identifying sequence variants associated with adverse drug effects, such as those for carbamazepine or statins. Similarly, there are genomic markers that efficaciously track the lack of response to or the optimal dosing of commonly used drugs, such as clopidogrel, steroid inhalers, warfarin, and pegylated interferon *(11)*. Multiple POC platforms are available for rapid genotyping (in <30 min). A randomized controlled trial has shown this strategy to have markedly increased the efficacy of treatment with clopidogrel for platelet suppression in patients undergoing coronary stenting *(12)*.

No More Needles

Although blood and urine represent the majority of the biological matrices sampled for bioanalysis, the need for repeated blood sampling in patients with chronic disease is disruptive and painful. Fortunately, 2 emerging approaches to wireless bioanalysis are pointing to a healthcare future that may not require needles.

The first approach involves replacing blood with fluids that are plentiful and easily obtained, including sweat, saliva, and tear film. The electrolyte content in sweat, for example, has been used to screen for cystic fibrosis and is being evaluated as a proxy for hydration status, which is potentially useful information for outpatient monitoring of congestive heart failure *(13)*. Similarly, salivary protein and microRNAs are being evaluated for drug metabolites such as phenytoin and as biomarkers for breast and oral cancer *(14)*. Through its ability to quantify capacitance, the common smartphone touchscreen is currently being explored as a direct salivary sensor capable of detecting toxins, drug metabolites, and biochemical signs of infection. The University of Washington and Microsoft Research are exploring LOC technology embedded within contact lenses to analyze glucose concentrations in tear film as a proxy for blood glucose *(15)*. Beyond having the glucose value shown on the contact lens directly, the data can be transmitted wirelessly to a receiving phone. A colorimetric assay can be embedded to change the color of the contact lens in response to the blood glucose concentration.

The second approach abandons fluid sampling altogether. The HemoGlobe, developed at Johns Hopkins University, is a smartphone-enabled sensor placed around the fingertip to optically measure the hemoglobin concentration (SpHb; Masimo)—information that could enable low-cost, noninvasive monitoring of anemia and acute bleeding. Sano Intelligence, a Silicon Valley–based startup, is developing an inexpensive, wearable sensor patch that can measure the components of a basic metabolic panel without blood sampling. If true, this "API [application–programming interface] for the bloodstream," as the company has positioned it, could be an important jump forward for noninvasively monitoring routine chemistries.

Implantable Diagnostics

In contrast to wearable patches and minimally invasive glucose monitors, LOC systems can operate as fully implanted sensors that use wireless communication to send and receive bioanalytical data from connected devices such as mobile phones and tablet computers. The advantages of using an implanted approach include assured proximity of the sensor to the tissue of interest, autonomous collection of physiological data, and continuous data collection that could provide more insight into a patient's physiology than episodic measurements. A trial that used an implantable device to deliver a peptide drug treatment for osteoporosis demonstrated that dosing could be administered remotely and wirelessly, and use of the device was correlated with improved bone density metrics *(16)*. By communicating with an implanted LOC sensor capable of proteomic and genomic analysis, smartphones could provide early warning for biochemical signs of rejection in patients with solid-organ transplants, of the appearance of circulating tumor cells, and of an impending myocardial infarction from the detection of circulating endothelial cells *(17)*.

Conclusion

Extraordinary opportunities clearly exist with mobile technologies, and these innovations will change the future of laboratory testing. Although wearable physiological sensors have garnered considerable attention to date, the next phase of wireless diagnostics will certainly be highlighting these new technological capabilities for unplugged laboratory medicine.

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