



A Glimpse into the Future of Diagnostics

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AQ:A-B In this issue of *Clinical Chemistry*, a report by the teams of Sam Sia (at Columbia) and Vincent Linder (at Claros/OPKO), together with a large group of collaborators, provides a remarkable example of what happens when one rethinks, both creatively and practically, how to collect diagnostic information in the developing world (1). By combining innovative engineering, a mixture of new and familiar technologies, good design, and careful attention to limited resources (human, financial, energetic), they have produced an integrated system whose impressive capabilities suggest a new approach to the design of portable diagnostic systems: keep the quality up (in fact, provide improved performance) relative to existing diagnostic technology; decrease costs; reduce the need for trained personnel; and use the web to move, store, and apply information.

AQ:C These goals constitute an aspirational roadmap for diagnostic systems for the developing world; this portable diagnostic system suggests that this roadmap can be followed practically.

But the significance of the work goes beyond the developing world. It represents one brick in what will surely be the foundation of a revolution that will fundamentally change the technical and business structure of diagnostics. The business model for diagnostics (as for many aspects of the medical systems of the developed world) is almost incredibly archaic in its treatment of information. It assumes that the primary value of diagnostic information is in defining the nature of disease, and the course of treatment, for individual, symptomatic patients. It also assumes that diagnostic information will usually be expensive and come from complex diagnostic technology managed and priced to maximize profitability. In this model, because information is expensive, it will be available only in cases of obvious need (i.e., for symptomatic disease). The most primitive issues of extracting value from masses of population-wide data, or even of handling the information relevant to a single patient, are only now beginning to be addressed.

Compare the way Google or Facebook (or the air-traffic control system, K-Mart, any telephone system, or Boeing) handle data with the way it is handled in almost any US hospital, and you get the idea: the medical system is arguably unique among high-technology industries in considering that bits of information should be expensive, and thus ensuring that information will be sparse. Almost everywhere else, information is considered essentially free, and the value and profit comes from its manipulation, storage, analysis, and use.

Imagine flying from Boston to Seattle on a plane in which the pilot had to insert a credit card into a slot and pay \$100 every time s/he wished to know the settings on the ailerons on the wings, or the location of the plane. Further, imagine that the airline operating the plane discouraged the pilot from buying relevant information until the plane was in danger of crashing. You'd often not make it to Seattle. That metaphor describes the current state of the use of diagnostic information in the US medical system. Sia and his group point to a way of thinking about diagnostics that fuses high-quality, low-cost, relevant medical information with an understanding that the value of that information might extend beyond the treatment of an individual patient.

The “Mobile Device”

The approach of Sia's group to diagnosis in the demanding circumstances of the developing world combines several components and ideas into a system that provides much greater value than any one of the individual components. The development of this system rests on several years of engineering development both by Sia and colleagues, and also by Vincent Linder and colleagues. Its elegance is not in the introduction of a radically new (and hence unproven) concept in bioanalysis, but rather in the development, combination, and integration of existing ideas:

1. Bioanalysis. It starts with a conventional ELISA (for HIV) that uses a cleverly simplified open-channel microfluidic chip to store reagents, to collect and introduce the sample of blood (1 μ L), to amplify the relevant biological signal (using silver-amplified detection), and to read out the result. This system, although based on familiar technology for immunoanalysis, was developed explicitly to simplify that analysis, to make

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human manipulations unnecessary in most of the analyses, and to contain costs.

2. Reader. This part of the system provides a second layer of innovation. It is well designed to be small enough to be easily portable and explicitly engineered to minimize its use of energy (to enable efficient use of batteries). Although a human is needed to collect the blood sample and to introduce it into the device (using a simple, practical sampler), the rest of the analysis is fully automated. This reader demonstrates how much function can be built into a low-cost device when the objective of the design is to simplify, and to lower cost, rather than to provide high-throughput analyses in a centralized clinical laboratory.

3. The Web. Most importantly, the reader is designed to carry out both the analysis and the reading autonomously, and to transmit the results—without further human intervention or interpretation—autonomously to a distant site such as a clinic for analysis or a national health-care registry for storage, epidemiological analysis, and other uses. This part of the system takes into account the fact that the shortage of skilled medical personnel is at least as serious a problem in the developing world as a shortage of money, and that the technology that is most rapidly transforming the developing world—technology that in some applications is developing more rapidly than in the developed world—is that of telecommunication systems, cell phones, and their derivative and supporting devices.

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The developers of this elegant, multifunctional system have also recognized that, in many settings, epidemiological evidence may be more valuable (and more actionable) than information about a specific patient. Knowing, for example, that a patient has dengue is not very useful to a healthcare worker; knowing that there is a local flare in dengue incidence allows public health officials to consider spraying to control mosquitoes.

This device (really, a “system,” because it combines clinical analysis, an interface to the web, and the integration of patient-specific, symptomatic diagnosis with seamless public health reporting) is an accomplishment in engineering and integration. The device uses, combines, and implements a number of areas of technology—microfluidics, ELISA, silver amplification, commercial electronics, industrial design, communication protocols, the web, the cloud—into a demonstration of what can be accomplished by innovation that uses existing technology. That this remarkable demonstration did not require a scientific invention of the magnitude of PCR or ELISA itself augurs well for its approach to clinical analysis. With the use of this style of eclectic systems design there is a lot more that can be done to reduce costs; to reduce the need for power,

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facilities, and skilled people; to incorporate other types of technologies designed for the developing world (2); and to take advantage of the staggering rate of advances in web-based information technology.

Implications for the Developed World

And what, if anything, does this report have to do with clinical analysis in the developed world? My opinion is: “A lot!” The US now spends 17%–18 % of its GDP on healthcare. At that expenditure rate, it has a healthcare system that is the most expensive per person in the world, but certainly not the most effective (in fact, by some measures, it is surprisingly ineffective) (3, 4). Diagnostics and clinical analyses, by themselves, are a relatively small part of this expenditure, but because these procedures determine the course of treatment, their indirect influence is large. The importance of the approach of Sia, Linder, and their groups has to do with the business model it suggests. In the US, diagnostics are based on a capitalist motivation: expensive tests, reimbursed separately as procedures, can be a good business. They can also (as in screening for prostate cancer by measuring prostate-specific antigen, and probably in routine mammograms in screening for breast cancer, and even the hallowed “annual checkup” with its battery of tests) lead to expensive, and sometimes poor, healthcare (5, 6). The technology required to provide information about populations for public health-based discussions (of diabetes, alcoholism, drug abuse, metabolic syndrome, immune status, nutrition levels, and other parameters used to design and test strategies for cost-effective medicine) look much more like the technology described here than that commonly found in clinical laboratories in the developed world.

And if this technology is intended to make biomedical information ubiquitous, inexpensive, and relevant both to individuals and to populations, who will pay for it? We don’t yet know. What is the value, to a society, of preventing or anticipating disease, relative to treating established illness? But the web is already there, and the technology described by Sia, Linder, and their groups, and by others, is a step toward making information about individuals—both ill and well, and both individually and collectively—more available and much less expensive.

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