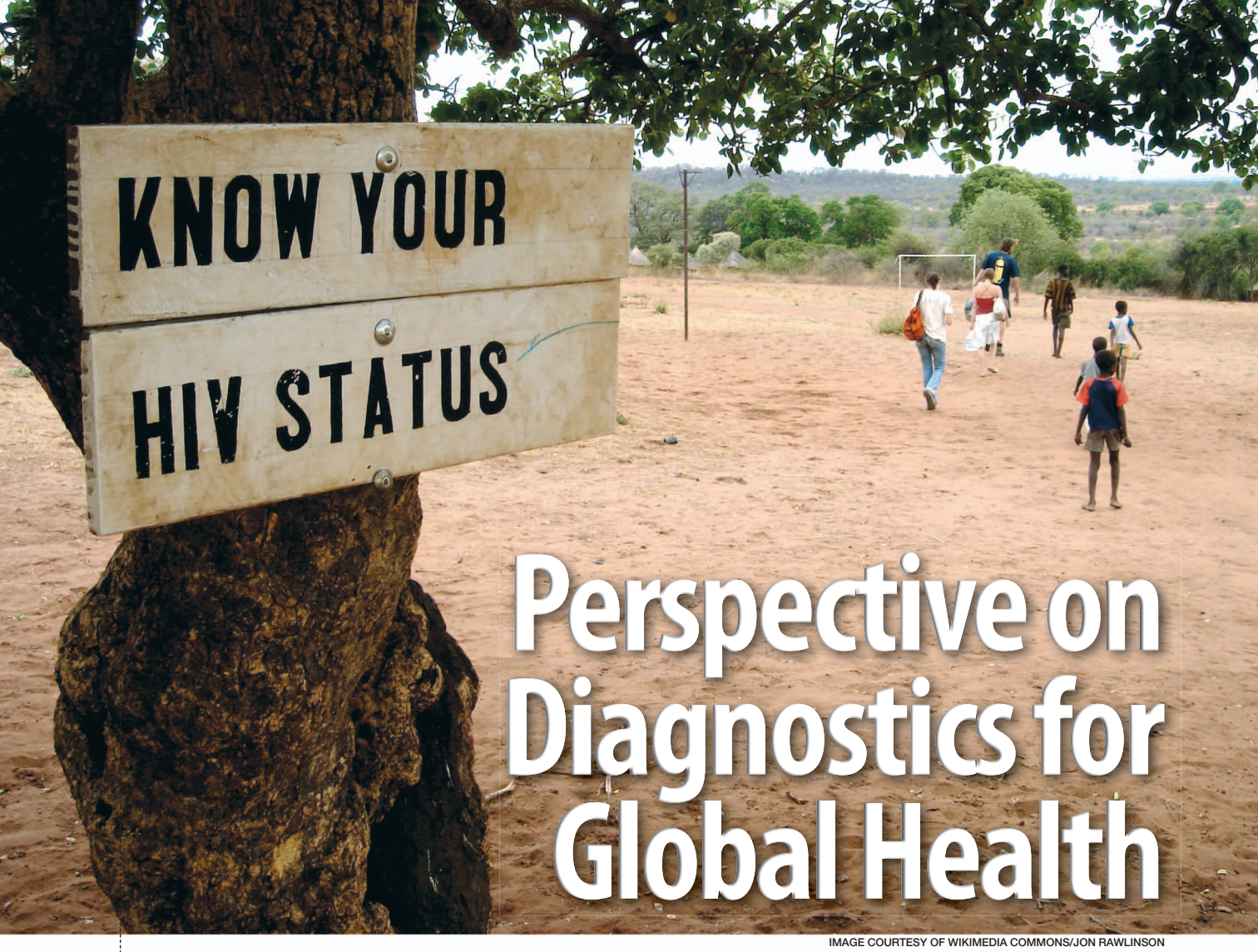

Perspective on Diagnostics for Global Health

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By Elain Fu, Paul Yager, Pierre N. Floriano, Nicolaos Christodoulides, and John T. McDevitt

Challenges in Evolving Chips-in-a-Lab to a True Lab-on-a-Chip

Diagnostic applications for global health have exploded in the past ten years. Numerous articles have been generated on global health priorities, constraints of resource-limited settings, and technological innovations for diagnostics development, including several comprehensive reviews [1]–[3]. In this article, we aim to provide 1) a focused summary of the most highly needed diagnostics, 2) a discussion of noteworthy recent developments of technologies in the field, and 3) a perspective on the evolution, challenges, and future directions of diagnostics for global health applications.

Need for Early Detection and Treatment

Disease treatment in the absence of a diagnostic test is often based on syndromic management (i.e., observing clinical symptoms and factoring in local prevalence of the disease). This situation can result in incorrect treatment of patients manifesting symptoms common to multiple diseases with local prevalence. Unnecessary treatment may compromise the patient (from harmful side effects of a treatment) or the community (through accelerated drug resistance, as has been found in

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the case of malaria [4]). Further, the patient remains untreated for the relevant condition, potentially leading to higher mortality and morbidity. A diagnostic test that can provide an accurate and timely diagnosis enables 1) earlier interventions before the appearance of advanced symptoms, 2) correct diagnosis and treatment for each patient, and 3) effective use of limited resources [4]. Thus, appropriate point-of-care (POC) diagnostics development for high-impact diseases can significantly reduce the global disease burden [4]–[6].

Unmet Needs for Diagnostic Tests

Health conditions can be divided into two broad categories (Figure 1), namely, infectious and noncommunicable diseases (NCDs). Infectious disease is a major cause of mortality in the developing world, killing nearly 15 million people each year [7]. A more comprehensive measure of disease burden is disability-adjusted life years (DALYs) and includes the effects of decreased quality of life due to disease [8]. An estimate from 2006 indicates that, for a core set of infectious diseases, the disease burden is an astounding 325 million DALYs per year [4]. Priority-infectious diseases, based on disease burden, are HIV/AIDs, tuberculosis (TB), and malaria [7]. Some progress has been made in developing POC diagnostic tests for HIV and malaria. However, there are still many unmet diagnostic needs. For example, in the case of TB, there is still no POC test appropriate for low-resource settings [9]. The gold-standard culture is highly sensitive and provides information on drug resistance but requires laboratory facilities and a long waiting time for results (e.g., ten days for rapid culture) [9]. Traditional microscopy is often used, but it requires a trained personnel and has a poor sensitivity of 70% [9] (Figure 2). High-performance nucleic acid amplification methods for the diagnosis of TB are commercially available now but are too expensive for use in low-resource settings (i.e., Cepheid GeneXpert is ~US$27,000 and ~US$30–US$85 per cartridge). With respect to HIV, CD4 counts and viral load testing remain as unmet needs that would have great value to inform treatment decisions (e.g., time to start antiviral therapy and monitoring the effectiveness of the therapy). In addition, a combined diagnostic for HIV and TB would be of value given the high rates of coinfection [9]. Within the set of neglected tropical diseases [10], there is an unmet need for an effective POC diagnostic for dengue/dengue hemorrhagic fever, human African trypanosomiasis, and leishmaniasis [9], [11]. The ability to simultaneously test for multiple disease conditions could be useful for the differential diagnosis of conditions with similar symptoms. Specifically, studies suggest that, in malaria-endemic regions, children presenting a fever but who do not have malaria often go without proper diagnosis and treatment, resulting in high mortality rates [12], [13]. Thus, a POC diagnostic that tests for a panel of fever-causing illnesses and could be adapted to a geographic area would have much value [9]. Additionally, a diagnostic for multiplexed detection of HIV, malaria, syphilis, and anemia would have specific utility for the care of women during pregnancy in the developing world [9]. In their recent review, Peeling and Mabey [9] have also highlighted the need for diagnostic tests for acute lower respiratory infections to determine the appropriateness of antibiotic treatment, and early diagnosis of the often asymptomatic sexually transmitted infections gonorrhea and chlamydia for proper patient treatment to reduce transmission.

Despite the disproportionate impact of infectious diseases in the developing world, NCDs are the leading cause of death globally, with almost 80% of deaths occurring in low- and middle-income countries [15]. For example, in 2008 there were 36 million deaths, 63% of total deaths globally, due to NCDs; the

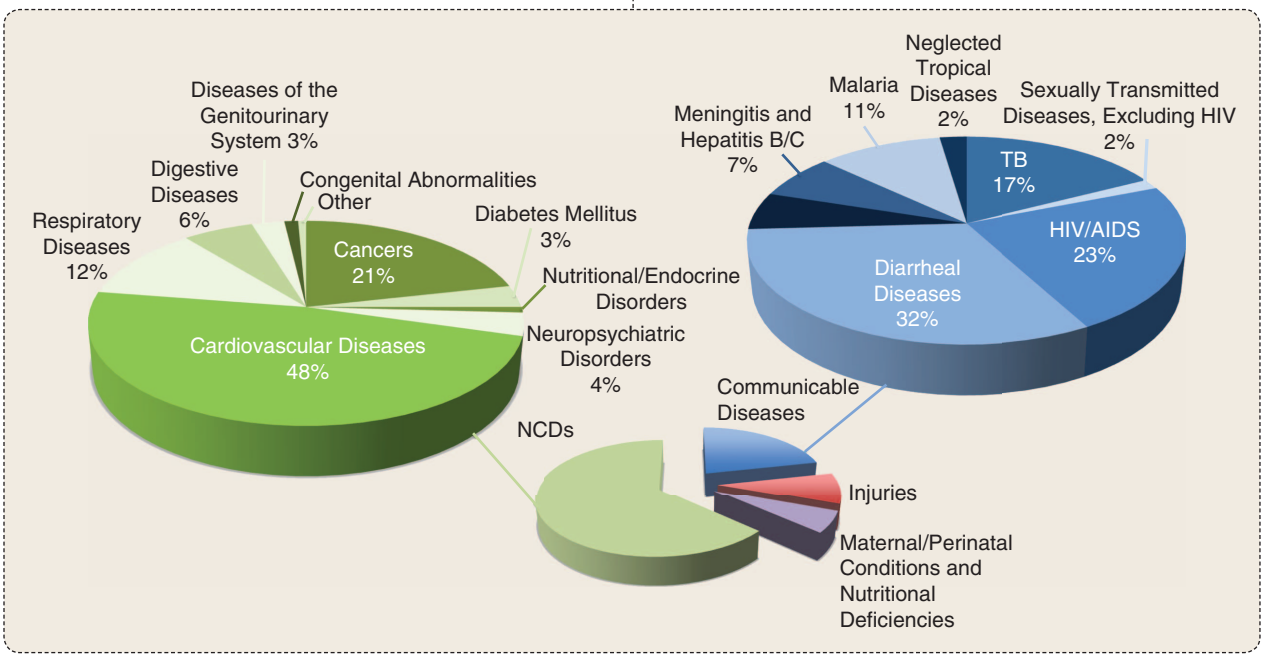

FIGURE 1 Worldwide percentage of mortality by health condition. The exploded pie chart shows the percentage of mortality in the four main categories of 1) communicable diseases, 2) NCDs, 3) maternal and perinatal conditions and nutritional deficiencies, and 4) injuries. A further breakdown of percentage of mortality worldwide for the categories of communicable diseases and NCDs is provided in the upper pie charts [14].

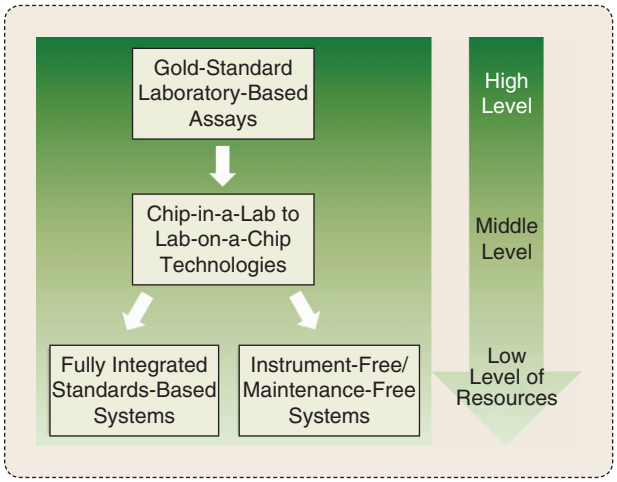

FIGURE 2 A schematic of the evolution of POC diagnostics development. The gold-standard laboratory assays are appropriate for settings with a high level of resources. There has been much progress in the development of promising chip-in-a-lab technologies that have, in some cases, been converted to true lab-on-a chip systems for use at the POC. However, the costs of the systems are often a barrier to their use in settings with lower levels of resources. One viable strategy is to push toward fully integrated standards-based systems that leverage the microelectronics and software industries. Also underway is a movement to create instrument-free diagnostics that will not only have a cost appropriate for the lowest-resource settings but will also fulfill the equipment-free requirement that is so critical to those settings.

predominant causes include cardiovascular disease (CVD), cancer, diabetes, and lung disease [15]. In the case of cancer, early detection of breast, cervical, colorectal, skin, and oral cancers, in particular, can lead to a reduction in mortality [15]. Additional NCDs of interest with respect to early diagnosis are gastrointestinal diseases and renal diseases, the latter being a related complication to both CVD and diabetes [15]. Early detection is especially compelling for certain NCDs (e.g., CVD and diabetes) because of the often simple behavioral interventions that can be implemented to improve health conditions [15].

The Continuing Challenge

Gold-standard diagnostic assays are often high-performance laboratory-based tests that require multistep protocols for complex sample processing. Tradeoffs for the high performance include long sample-processing times, long periods of time for samples to be transported to the laboratory and for the results to be transmitted back to the patient/caregiver, the need for trained personnel to run the test and interpret the results, and the need for specialized instrumentation for processing samples and detecting analytes. Also assumed is the access to electricity to power the instrumentation, maintain strict environmental conditions, and refrigerate reagents until use in the assay. The requirements of laboratory-based tests are often incompatible with the constraints of resource-limited settings. Constraints in these settings include patients with limited access to clinics and contact time while being there, limited training of test providers, lack of laboratory facilities and testing environments with uncontrolled temperatures and humidity levels, and limited local infrastructure, including a lack of cold chain for refrigeration of reagents [1], [2], [4]. The World Health Organization has coined an acronym for the characteristics of POC diagnostics that are appropriate for even the lowest-resource global health settings: affordable, sensitive, specific, user friendly, rapid and robust, equipment free, and deliverable to users (ASSURED) [16]. Thus, the overall challenge has been and continues to be to create high-performance assays that are appropriate for the various multiconstraint settings relevant for global health applications, including the lowest-resource settings.

Dedicated Global Health Lab-on-a-Chip

While significant progress has been recently made in genomics, proteomics, and other disciplines, few of the scientific discoveries have impacted clinical practice globally [17], [18]. There is a strong potential to leverage these discoveries for a broad impact in diagnostics for global heath applications using chip-based approaches. An important trend relevant here is the miniaturization of designs afforded by the small dimension scales of microfluidic-based devices. This allows for portability and the use of small sample and reagent volumes. These also enable rapid POC results at the bedside, in the ambulance, or at other remote locations [19]. The lab-on-a-chip (LOC) technology is often configured with a permanent instrument and disposable cards. The instrumentation can often be battery powered, and the cards can incorporate reagents stored in dry form to remove the immediate need for a power grid. Automation of the processes results in the ease of use for minimally trained users. In many cases, the cards can be affordable for the specific setting when scaled up for high-volume manufacturing. Key steps have been reached by numerous LOC efforts, and important goals are defined with the micro total analysis system (μTAS) paradigm. These have led to technologies suitable for dedicated global health applications at the POC, in genetic [20], [21]; proteomic [22], [23]; and cellular testing [24]–[26]. Yet, very few complete workable POC clinical devices have emerged despite tremendous progress in microelectromechanical systems (MEMS), microfabrication, microfluidics, and related areas [17], [18]. Indeed, while the core of typical LOC systems is substantially smaller than that of the bench-top counterparts, they still rely on a network of macroscopic laboratory-based infrastructure for sample processing, sample introduction, analyte detection, data processing, and reagent handling, thus limiting their utility for POC applications. The selected examples of LOC approaches described below highlight efforts to address the challenges of evolving from chips-in-a-lab to a true LOC.

The Yager group [27] has developed a microfluidic flow-through membrane immunoassay, featuring gold-antibody conjugates stored in dry form on a disposable laminate card, which works in conjunction with external pumping and imaging instrumentation. The system, demonstrated for the malarial antigen *Plasmodium falciparum* histidine-rich protein II (PfHRP2), retained high activity after a 60-day storage at elevated temperatures, with a detection limit in the subnanomolar range and a time to result below 9 min. Other approaches by Sia with MEMS and Singh using chip-based separation and quantitation have continued to increase the level of integration of diagnostic devices [28], [29].

Significant progress has been achieved in fluid handling through the implementation of innovative LOC components and actuation strategies. Another example by the Sia group demonstrated the actuation of multiple microfabricated microvalves with rapid response in an enzymatic assay via liquid-filled control channels in a handheld instrument powered by a simple 9-V battery [30].

Madou et al. have demonstrated the use of microfluidic compact disc (CD) formats [31] as a cost-effective approach to eliminate pumps, tubing, and valves, and drive fluids with centripetal force. Recently, the Liu laboratory [32] have applied this approach in detecting microparticles and cells. The device, compatible with the use of standard CD drives, was demonstrated with Chinese hamster ovarian (CHO) cells of various concentrations and could eventually be employed to perform enzyme-linked immunoassays (ELISAs). In a recent perspective article on optical biosensors, Ligler highlights the innovations that may lead to faster, smaller, and more cost-effective optical biosensor systems. Among the most promising example for facilitating integration is a new generation of polymer components, e.g., organic photodiodes (OPDs), for use as optical detectors [33].

The work done by Klapperich and coworkers has shown the suitability of plastic microfabrication methods, compatible with global diagnostics costs, to produce high-performance parts for use in continuous-flow polymerase chain reaction assays [34]. This approach may have a significant impact in the diagnosis of infectious diseases in the developing world and also can provide a cost-effective approach to DNA testing that resonates with the promise of personalized medicine in developed countries to drive down the cost and improve health care [20], [21].

Magnetic nanotechnology has been recently used to enable rapid, multiplex immunoassays for POC applications. The portable battery-powered platform, developed by the Wang laboratory [35], also has reduced requirements for operator training. Their approach has provided promising analytical results using p24 protein as a model. It is envisioned that, when demonstrated with clinical samples, this technology could be used to detect a number of infectious disease agents such as HIV, Hepatitis C virus, *Mycobacterium tuberculosis*, *Salmonella typhi*, toxigenic *Escherichia coli*, as well as swine (H1N1) flu and avian (H5N1) flu (Figure 3).

A Fully Integrated Standards-Based Systems Approach

Another viable strategy to reduce instrumentation costs for resource-limited settings, which is in development in the McDevitt laboratory, is to leverage the capabilities of a global network of diagnostic devices based on universal standards. This new approach is a significant departure from current diagnostic test systems that are fragmented in terms of specialized instruments dedicated to

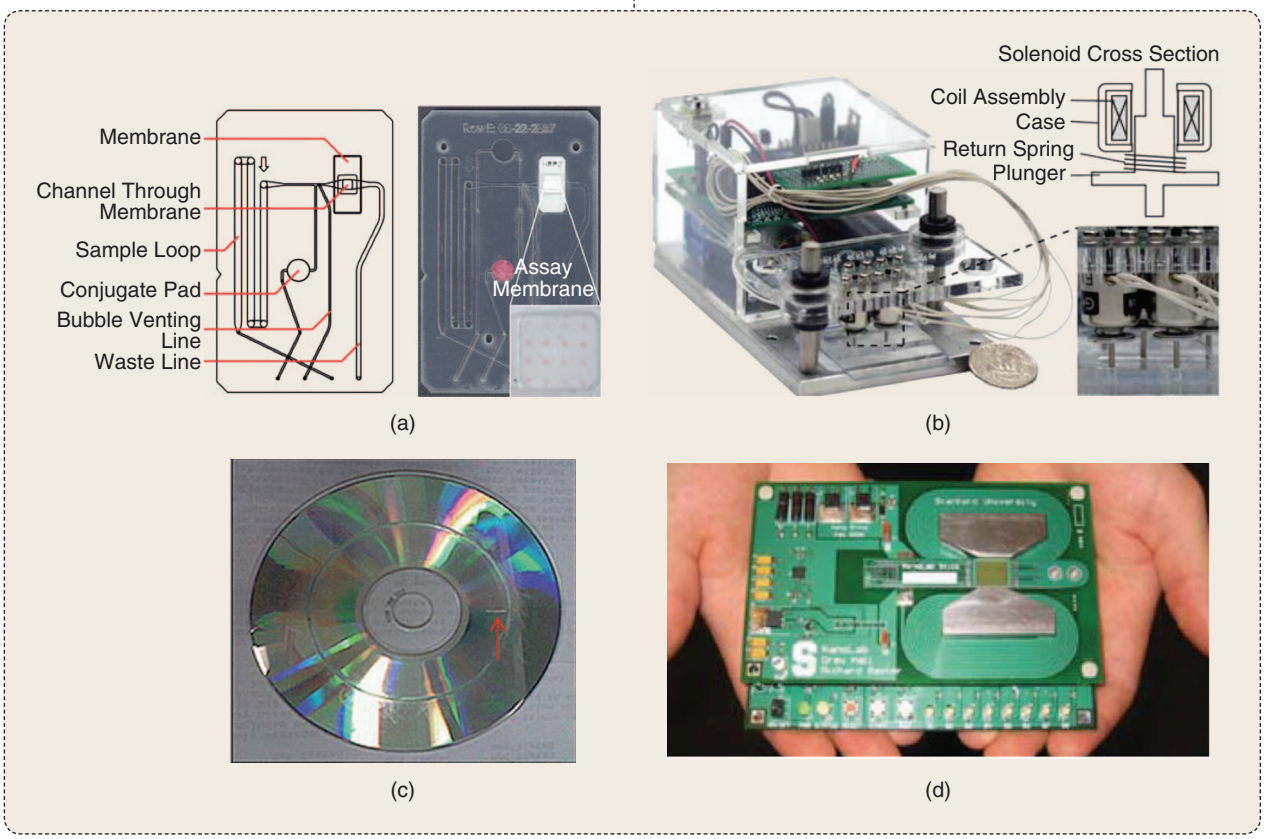

FIGURE 3 Examples of promising LOC technologies. (a) Microfluidic flow-through membrane immunoassay developed in the Yager laboratory achieves rapid and sensitive detection using dry reagents stored on the disposable card [27]. (b) The Sia laboratory has demonstrated higher-level integration that is completely battery powered [30]. (c) A CD-based approach for cell detection from the Liu laboratory reduces the requirements for pumps and valves [32]. (d) The Wang laboratory has developed a wash-free multiplexed immunoassay based on magnetic nanotechnology [35]. (All reproduced with permission from the Royal Society of Chemistry.)

Test	Gold Standard	P-BNC Chip Type	Sample Type	Results
CD4 HIV Immune Function	Flow Cytometry	CPU 2 	Drop of Whole Blood	R^2 = 0.93–0.95 (N = 200)
Oral Cancer (OSCC)	Pathologist	CPU 2 	Brush Biopsy	AUC = 0.97–1.00 (N = 52)
Cardiac AMI	CTnI, Myo, CK-MB*	CPU 1 	Oral Swab	AUC = 0.94–1.00 (N = 100)
Roadside Drug Tests	LS-MS/MS**	CPU 1 	Oral Swab	R^2 = 0.926 (N = 45)

* cardiac troponin I (CTnI), myoglobin (Myo), and creatine kinase-muscle type, brain type (CK-MB).
** liquid chromatography-tandem mass spectrometry.

FIGURE 4 The McDevitt group has developed a fully integrated programmable PBNC platform that enables new test configurations to be quickly adapted, developed, and applied for a variety of diagnostic indications through the insertion of molecular level code (or disease-specific reagents).

specific analytes as well as specific geographic and demographic sectors. For example, today, the five most active POC sectors globally are diabetes, acute coronary syndrome (ACS), coagulation, HIV, and platelet function [36]. For the area of cardiac heart disease alone, there are three major sectors involving risk, heart attack detection, and congestive heart failure with at least two qualitative and eight quantitative rapid whole blood devices deployed in POC and remote laboratory settings [36], [37].

The programmable bionanochip (PBNC) system is inspired by the microelectronics industry, in which a standard operating system is used in conjunction with modular software programs specific to a variety of applications, to provide significant cost reductions and produce increasing performance (Figure 4). The PBNC system is a platform that enables new test configurations to be quickly adapted, developed, and applied for a variety of diagnostic indications through the insertion of reagent-specific molecular level code [38], [39]. As such, the PBNC system has the capacity to serve cell counting, typing, and differentiating functions [40]–[42]. Alternatively, PBNCs can complete analysis of chemical, genomic, and proteomic analytes using bead-based microreactors [43]–[52].

These two distinct PBNC assay platforms are packaged within a disposable, single-use injection-molded plastic laboratory card comprised of a network of microfluidic components for the complete transfer and processing of biological samples. These sensors provide quick and accurate information on cellular, genomic, or proteomic biomarkers of disease at the POC. All assay steps are conducted without human intervention within the laboratory card that sits within an analyzer equipped with a light-emitting diode (LED)/charge-coupled device (CCD)-based detection system and mechanical actuators. This approach eliminates the need for external fluidics such as pumps, tubing, and connectors. The assay is performed through a sequence programmed into the controller of the analyzer with control over the flow rate, incubation time, and reagent wash achieved by the actuation of stepping motors that direct the fluid flow through the depression of fluid pouches. The sample is directed to an on-chip waste reservoir, and the entire biochip can be discarded as solid waste after the assay, facilitating biohazard waste management.

The bead-based PBNC is now moving through six major clinical trials and has been successfully applied to serve a variety of important health applications, including ovarian, prostate and oral cancer screening and monitoring [47], [48], [53], cardiac risk assessment [44], [45], and diagnosis of acute myocardial infarction (AMI) [51]. Compared with gold standard and laboratory-confined methods, most of which are based on ELISA methodology completed in bulky and expensive instruments, the miniaturized bead-based PBNCs exhibit assay times in minutes instead of hours, limits of detection two or more orders of magnitude lower [38], and a proven capacity to multiplex [38], [39], [43]–[45]. Likewise, the PBNC sensor may be programmed to detect various panels of target proteins, antibodies, toxins, and drugs of abuse in biological fluids.

The membrane-based PBNC serves as a miniaturized analysis system that mimics flow cytometry instrumentation in their capacity to complete important cell-counting applications, such as HIV immune function testing using CD4 cell counts [42]. In addition to lymphocyte enumeration in resource-limited settings, the same membrane system is now being applied for oral cancer screens for the analysis of minimally invasive brush biopsies of oral mucosal lesions [47], [48]. Here, cytomorphometric data and information about the relevant expression of molecular biomarkers of malignant potential are acquired in an automated manner using refined image analysis algorithms based on pattern-recognition techniques and advanced statistical methods. This dedicated PBNC approach has the potential to turn around biopsy results in a matter of minutes as compared to days for traditional pathology methods.

Most importantly, the results achieved with the PBNC system correlate well with those of high-performing but laboratory-confined methods. This is a feature that, when considered along with the system's modularity and advanced performance

characteristics in multiplexed capacity mode, promises to remove one of the main barriers for the ultimate acceptance and implementation of POC testing. These tests no longer have to be associated with high cost and limited performance.

Toward Instrument-Free Devices for the Lowest-Resource Settings

An especially compelling need in the lowest-resource settings is for equipment-free diagnostics, such that ongoing maintenance and repair are not required. A major challenge in creating a diagnostic device that is free of dedicated equipment is how to transport fluids within the device without the commonly used active pumping systems. The Delamarche group has developed a microfluidic capillary system with autonomous pumping capability [54]. Their silicon/polydimethylsiloxane (PDMS) microchip performs a conventional sandwich format assay on C-reactive protein (used as an indicator for myocardial infarction) using a single-step delivery of sample and conjugate (similar in operation to the chemical delivery steps in a conventional lateral flow strip test) with fluorescence-based detection [55], [56].

Capillary pumping is the method of fluid transport in the simple lateral flow tests that have been used in low-resource settings for decades. Though lateral flow tests fulfill many of the ASSURED criteria, they have been criticized for both their inability to multiplex (i.e., assay for multiple analytes from a single biosample) and their lack of sensitivity for many analytes of clinical importance [57], [58]. In 2008, the Whitesides group pioneered the use of microfluidic paper-based analytical devices (μPADS), two- and three-dimensional paper-based structures that enable colorimetric assays (e.g., for detection of glucose and protein) with multiplexing capability [59], [60]. The original μPAD structures were created by photolithography [61], but since then numerous alternative fabrication methods have been demonstrated, including wax printing [62], [63], cutting [64], and ink-jet printing [65]. Additional work in the area of paper-based assay development has focused on implementing multiplexed assays for the detection of additional biomarkers using one-step colorimetric reactions (e.g., nitrite, uric acid, and lactate) [66], [67] or performing the simultaneous analysis of multiple controls for on-device calibration [68]. Alternative detection methods in paper-based assays have been investigated, including electrochemical detection from screen-printed electrodes for metabolites and heavy metal ions [Pb(II) and Zn(II)] [69]–[71].

The second limitation of lateral flow devices is their inability to perform the controlled manipulation of multiple reagent volumes in a timed sequence of sample-processing steps characteristic of high-performance gold-standard assays. Recently, the collaboration of Yager, Lutz, and Fu [89] has addressed this issue, demonstrating two-dimensional paper networks (2DPNs) for autonomous multistep sample processing. A key feature of the 2DPN assay is the configuration of the network, composed of multiple inlets per detection region, which functions as a program for the timed delivery of multiple reagent volumes within the network. The 2DPNs that perform the processes of signal amplification [72], sample dilution and mixing [73], and small molecule extraction [73] have been demonstrated. Critical to the operation of multistep paper-based assays is a set of paper fluidic tools, i.e., analogs to the pump controls and valves of conventional microfluidics, to manipulate fluids within the network for precise timing of reagent delivery and metering of reagent volumes [72], [74], [75]. Additional tools for controlling flow via modification of the wetting properties of the paper channel [76] and simple user-activated mechanical on switches [77], [78] have been demonstrated by the Phillips, Whitesides, and Shen groups.

Also, integral to the development of ASSURED diagnostic devices is to have available robust methods for power-free temperature control. Recently, the Weigl group at the Program for Appropriate Technologies in Health (PATH) has demonstrated the use of chemical heating, e.g., hydration of CaO, and phase-change materials to perform loop-mediated nucleic acid amplification [79]. Their device achieved a controlled elevated temperature of 65 $\pm$1.5 °C for over an hour [79]. The specific combination of exothermic reactants and the composition of the phase-change material can be used to tune the thermal properties of the instrument-free heater for numerous applications, including other isothermal nucleic acid amplification methods [80], cell lysis protocols, and sample concentration methods based on temperature-responsive polymers [79].

A particularly challenging issue is how to achieve high-sensitivity or quantitative detection without dedicated instrumentation. The use of a dedicated reader in conjunction with nonvisible labels, e.g., fluorescent or magnetic particles, has been a common strategy for improving the sensitivity of conventional lateral flow tests [81], [82]. Use of a dedicated reader has also been employed for the measurement of analyte levels and quantitative readout. For example, the Whitesides group has demonstrated the use of a transmission-based reader for measurements in index-matched paper devices [83]. Alternatively, there are several commercially available readers for lateral flow tests that provide quantitative readout of fluorescence or colorimetric detection [81]. The ubiquity of cell phones (possessed by approximately 60% of people globally [84]), even in low-resource settings, provides an opportunity for higher-capability assay readout without a dedicated instrument. The use of cell phones for the acquisition, analysis, and transmission of assay data is an area of active research and development. Challenges include the acquisition of high-quality image data, given the expected wide range of lighting conditions and user variability of camera positioning [85]. The Whitesides group has demonstrated the use of a cellphone camera for direct acquisition of endpoint intensity measurements from a colorimetric paper assay [86], while the Shen group has demonstrated quantitative detection of chemiluminescence [87]. A related approach has been to develop an adapter module to interface a standard cell phone. The Ozcan group has developed a compact adapter (28 g) consisting of LEDs, lens, and filter, which couples to a cell phone camera for wide-field fluorescent and dark-field imaging capability [88] (Figure 5).

Challenges and Future Directions

Specifications Must Meet User Performance Requirements

Some technology developers have been arguing that having access to a poor-performance POC diagnostic test is better than having no diagnostic test at all. This is demonstrably false in some cases: introduction of a diagnostic test with substandard

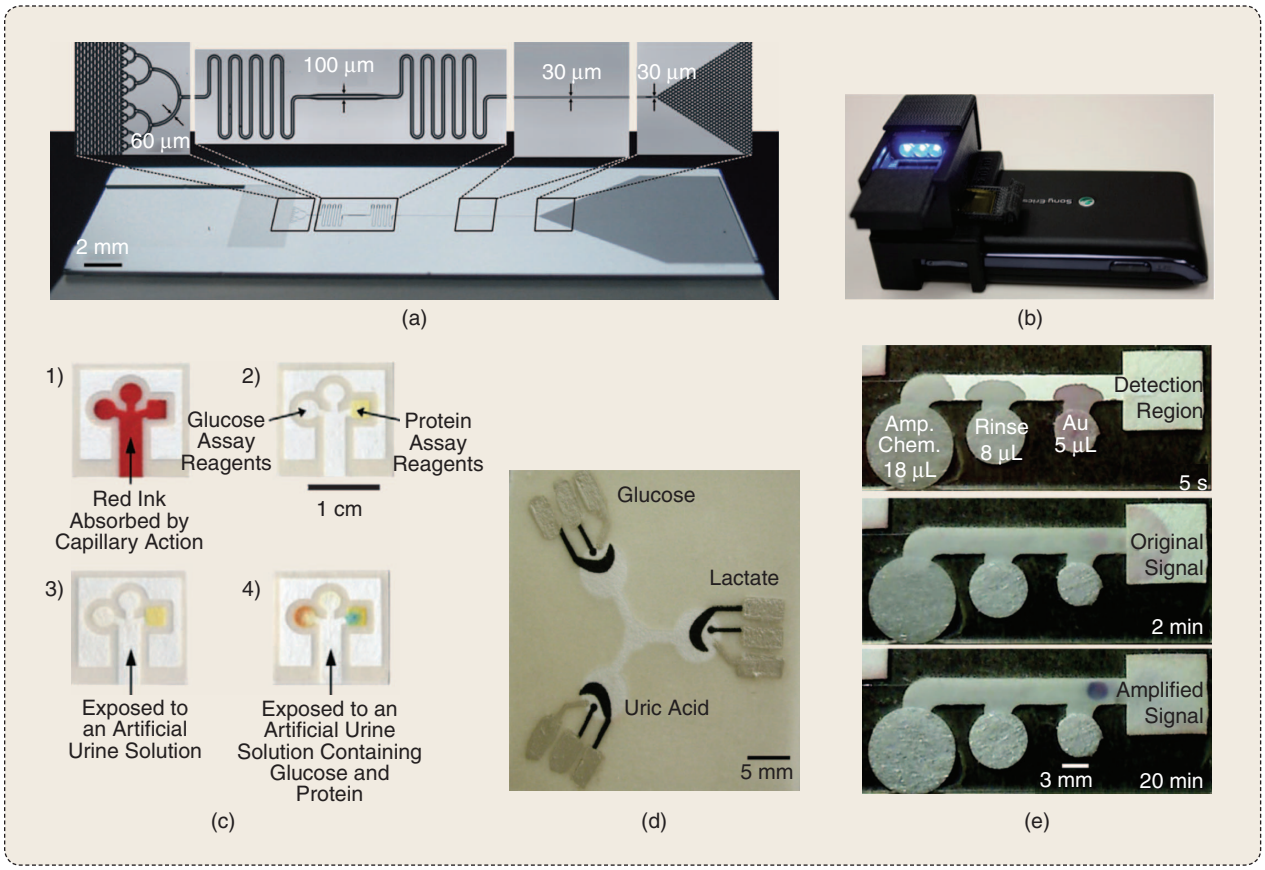

FIGURE 5 Examples of noteworthy technologies in the movement toward diagnostic devices that are free of dedicated instrumentation. (a) The Delamarche group has developed capillary-based microfluidics in a hybrid silicon/PDMS device for the pump-free manipulation of fluids [56]. (Reproduced with permission from the Royal Society of Chemistry.) (b) The Ozcan laboratory has demonstrated the use of a compact adapter that couples to a cell phone for fluorescence and dark-field imaging of assay results [88]. (Reproduced with permission from the Royal Society of Chemistry.) (c) The Whitesides laboratory has developed μPADs for multiplexed detection in paper assays [59]. (Reprinted with permission from John Wiley and Sons.) (d) The Henry laboratory has developed electrochemical detection in paper using screen-printed electrodes. (Reprinted with permission from [69]. Copyright 2009 American Chemical Society.) (e) The 2DPNs for autonomous multistep sample processing and higher performance assays have been demonstrated by the collaboration of Yager, Lutz, and Fu [89].

performance specifications can have significant adverse consequences. For example, the case of poor sensitivity of rapid lateral flow tests for influenza has been highlighted recently. Those tests generally have an acceptable clinical specificity (the number of positive cases as measured by the diagnostic test divided by the total number of true positive cases as determined by a gold standard test) of >90% but have poor clinical sensitivity (the number of negative cases as measured by the diagnostic test divided by the total number of true negatives as determined by a gold standard test) of 11–70% [90]–[93]. Low clinical sensitivity translates to false negatives, and, thus, missed opportunities to appropriately treat patients suffering from influenza with antiviral medication. The U.S. Center for Disease Control issued a statement during the influenza pandemic of 2009 that recommended discontinuing the use of those tests [94]. From the previous example, it is clear that an important factor in determining the required performance specifications for a given diagnostic test is consideration of the consequences of obtaining a false-negative or false-positive result with that test. The consequences of cases missed because of implementing a low-clinical-sensitivity diagnostic test can be severe in the context of an acute health condition with a high mortality rate. On the other hand, the consequences of implementing a low specificity diagnostic test (and the resulting high rate of false positives) can be equally problematic with respect to exposing the misdiagnosed patient to a treatment with potentially adverse side effects, undue emotional stress, and the financial burden to the health-care system of additional testing or unnecessary treatment. The latter case was highlighted recently in the context of prostate cancer screening. A false-positive result for the serum prostate-specific antigen test impacted at least one in eight men repeatedly screened [95], and has resulted in unnecessary procedures and expense to the health-care system.

Also critical to understanding the required performance specifications of a potential diagnostic test is prevalence of the disease in the population targeted for screening. The utility of a diagnostic test in a population with a given disease prevalence can be quantified by positive and negative predictive values, the proportion of positives as measured by the diagnostic test that are true positives and the proportion of the negatives as measured by the diagnostic test that are true negatives, respectively. Thus, a diagnostic test with given clinical sensitivity and specificity will have a higher positive predictive value in settings with a higher

disease prevalence, while the test will have a lower negative predictive value in settings with a higher disease prevalence. This makes clear the importance of targeted use of a diagnostic test in the most relevant populations.

Future Challenges

Rational diagnostics development for a particular health condition must begin with a thorough understanding of user requirements in the intended setting [4]; the next step is to apply a technology that can meet those user requirements of performance, ease of use, shelf life, tolerance for maintenance of instrumentation, and cost. Given the wide range of resource levels in global health applications [1] as well as varied requirements for performance that are specific to a biomarker and health condition, it is unlikely that any one technology will be appropriate for all global health applications. However, the use of numerous specialized tools, each tailored for a single diagnostic indication, also creates a challenge in terms of managing multiple tools, maintaining a supply chain, and training end users to handle multiple diagnostic aids. This dichotomy will be a central challenge for the next decade.

There are additional factors that will contribute to the success or failure of particular diagnostic tests in getting to market and to the intended end users. For example, there is generally a higher success rate for diagnostic tests that can be applied to large populations [33], such as tests with the added value of multiplexing for cost-effective testing. However, the regulatory processes for the approval of multiplexed diagnostic tests are less understood than for diagnostic tests dedicated to single measurements [96], [97]. In addition, devices for detecting more than one biomarker may suffer from a limited understanding of their relevance to the particular disease, and a resulting lack of physician awareness and backing, and/or resistance from health-care stakeholders to reimburse, especially in the cases of prevention and early diagnosis [33]. Further, diagnostics development activity in private industries has emphasized the developed rather than the developing world, resulting in the production of instrumentation that is complex and cost prohibitive to use in resource-poor settings [5].

Recent efforts in diagnostics development for global health applications are beginning to produce solutions that could be used in the low-resource setting of developing countries. In particular, diagnostic devices that are free of dedicated instrumentation have the potential to be affordable (and maintenance free) for even the lowest-resource settings. Another viable approach is to define and address the requirements of resource-limited settings in developing high-performance methods for a suite of disease applications on a common platform. With this standards-driven approach, inspired by the software and microelectronics industry, there is a strong potential to sustain the capital expansion that exploits the health-care infrastructure of developed countries while bringing the same tools to end users in the developing world.

The total LOC-based biochip market was US$2.4 billion in 2009 and is projected to increase to US$5.9 billion in 2014 [98] (part of the increasing POC market that is estimated to reach more than US$18.7 billion by 2011 [99]). This should be a powerful incentive for commercial efforts to move toward true global health solutions. The recent U.S. health-care legislation debate and consensus for reform provides additional momentum with the recognition that POC, now representing most of the growth in the in vitro diagnostics sector [100], can deliver lower costs while improving the health of patients.

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