INVITED PAPER

Microfluidics and Nanotechnology for Detection of Global Infectious Diseases

This paper reviews the state-of-the-art technologies for detection of HIV, malaria, and TB, and discusses opportunities and future prospects.

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ABSTRACT | Infectious diseases remain among the world's leading causes of mortality and years of life lost. Significant attention has been paid to the "Big Three" infectious pathogens—human immunodeficiency virus (HIV), malaria, and tuberculosis (TB)—but other conditions such as Chagas' disease, dengue, Ebola, and typhoid, as well as multipathogen processes such as viral hepatitis, pneumonia, and diarrhea, also have major global impact. Addressing these significant disease burdens, which disproportionately impact the world's poorest regions, is a multifaceted grand challenge, requiring new solutions and new technologies. Diagnostics enabled by advances in microfluidics and nanotechnologies can be an important part of the solution. Advantages such as smaller sample size, increased sensitivity, and new multiplexed sensing modalities in a point-of-care format can allow rapid dissemination of test results in remote and resource-limited regions. In this review, we provide a critical assessment of the state-of-the-art in use of these technologies for detection of HIV, malaria, and TB. In addition to discussing opportunities and future prospects, we also discuss the need for additional governmental and nongovernmental funding sources to develop these technologies to their fullest potential, and the need for new business models to enable their commercialization and deployment.

KEYWORDS | Biosensors; diagnostics; global health; HIV/AIDS; infectious diseases; malaria; microfluidics; nanotechnology; point-of-care; tuberculosis

I. INTRODUCTION

Infectious diseases continue to be a major factor in an increasingly complicated global public health picture. The "Big Three" pathogens span the spectrum of basic microbiology: a virus (HIV), a parasite (*Plasmodia* spp., which cause malaria), and a bacterium (*Mycobacterium tuberculosis*). Alongside dozens of other pathogens, these infectious agents represent critical challenges to global public health, including the vision espoused by the Millennium Development Goals for social and economic well-being nearly 15 years ago [1]. Fig. 1 and Table 1 summarize the impact of major infectious diseases worldwide, and indicate the countries bearing the largest burden of HIV, malaria, and tuberculosis (TB), clearly depicting how disproportionally countries among the world's poorest and most resource-limited regions are affected.

The approach to global control of these infectious pathogens, as well as numerous other infectious diseases that are endemic or resurgent, has three battlefronts. First, since most of these conditions have roots in poverty, inequality, and environmental degradation, efforts promoting economic and environmental health and social equality are key to eliminating the risks of acquiring infectious diseases at their source.

Second, the impact of antimicrobial drugs and vaccines targeting global infectious disease has been staggering. Conditions such as smallpox, polio, and dracunculiasis (guinea worm disease) have been nearly eliminated

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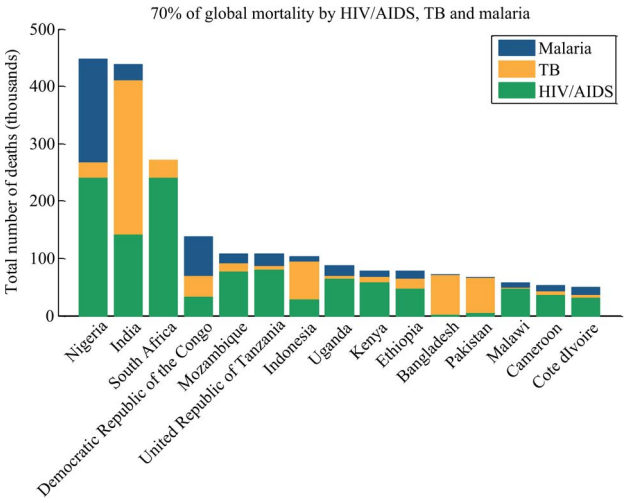

Fig. 1. ***The impact and burden of major infectious diseases. Based on 2012 causes-of-death data available from the WHO, the bar chart depicts country-specific mortality data only for HIV, TB and malaria. These 15 countries bear more than 70% of the global mortality associated with these three pathogens. Source: [58].***

globally by effective vaccines, while measles, mumps, diphtheria, tetanus, yellow fever and a handful of other pathogens have been effectively—though not completely—contained. At the same time, in the nearly century-old antibiotic era, potent drugs have saved countless lives, including in developing countries, 22 million people with TB [2], 5.5 million people with HIV [3], and more than 1 million malaria-infected children under five [4] in the last 15 years alone. New treatments for hepatitis C have raised a glimmer of hope for global control of this scourge, which affects nearly 200 million people [4]. Despite these successes, many challenges remain: antimicrobial drug resistance is at crisis levels; many pathogens such as Chagas' disease, dengue, and Ebola lack effective drugs or vaccines altogether; and the delivery of existing, effective interventions remains woefully inadequate.

Table 1 2012 Global Mortality

Cause of death	Global burden
Lower respiratory infections	3,051,318
HIV/AIDS	1,533,760
Diarrhoeal diseases	1,497,674
Tuberculosis	934,838
Malaria	618,248
Meningitis	395,225
Acute hepatitis B	149,162
Measles	130,461
Syphilis	78,910
Encephalitis	77,870
Whooping cough	67,061
Tetanus	66,131
Leishmaniasis	48,405
Acute hepatitis C	38,913

The third front in the global war on infectious disease is the battle for accurate diagnosis. Accurate diagnostic technologies for use at or near the point of patient care can have a profound impact on the control of global infectious diseases. Yet, in this emerging era of personalized medicine, high-throughput genome sequencing, and laboratory and imaging technologies of unprecedented power and sophistication, most of the world's population has little or no access to basic diagnostic tools, including hematology and chemistry analyzers, electrocardiograms, X-rays, and CT scans [5]. According to a recent study conducted by the RAND Corporation, access to simple, affordable diagnostic tests for just four conditions—bacterial pneumonia, malaria, syphilis, and TB—could save millions of lives each year [6].

Importantly, successful implementation of diagnostic tests for global infectious disease will require technologies—and ultimately, commercial products—with critical attributes: low cost, simple to use, compact and portable, quality-assured, and accurate. The emergence of microfluidics and nanotechnologies suggests that many diagnostic products with these attributes are within reach. Here we examine the ways in which the tools of the submillimeter scale may address the shortcomings of what is currently available, and what may be the key to realizing a long held, but not yet fulfilled promise, to meet the needs of people worldwide for simple, accessible diagnostic tests.

II. THE MICROFABRICATION AGE

The silicon era, born with the transistor in the 1940s, introduced processes for precise fabrication of submicron features. The rapid emergence of silicon-based microelectronics enabled vast computational power to be contained in tiny integrated circuits, which has brought information processing into small-scale devices and instruments. In parallel, the plastics era, heralded by the development of bakelite in the 1910s, has enabled mass production of precise, robust products of increasing complexity and low cost.

One recent outgrowth of the age of microfabrication in silicon and plastic has been the application of these materials and the underlying engineering methods to biomedical problems. Medical devices from insulin pumps to pacemakers to glucometers have been made possible at mass scale by applying microscale fabrication and processing methods utilizing silicon semiconductor and plastics manufacturing industries to medical problems.

Diagnostics are the most recent biomedical field to make use of advances in silicon and plastics engineering. A new paradigm is emerging in which mass produced, low cost, ultra-portable instrumentation with sophisticated sample and information processing capabilities can provide answers to medical diagnostic questions far from laboratory facilities. New fluid handling and sensing modalities have emerged that enable the manipulation and interrogation of tissues and fluids like blood, urine, and saliva, which can be

used to identify major infectious agents, their molecular signatures, and the body's response to them. Synergies with mobile communications infrastructure can also be leveraged for so-called "point-of-care" deployment of portable diagnostic technologies.

As a result, many conditions that have been undiagnosable in hard-to-reach settings will now be diagnosable, alerting patients and health workers to the need for specific, available treatments. The impact of a new generation of diagnostics is beginning to be felt in areas of the world hardest hit by HIV, TB, and malaria [6], [7].

III. ASSESSING THE CURRENT STATE OF GLOBAL HEALTH DIAGNOSTICS

The underlying biology of infectious diseases is at the heart of the opportunity and the challenge of developing new diagnostics. The workhorse of current global infectious disease diagnosis: the *rapid lateral flow immunoassay* and related methods, often termed a "Rapid Diagnostic Test" or RDT, takes advantage of components of the pathogen or host-generated antibodies to diagnose infection. But not every pathogen behaves in a way that allows for RDT-style detection, and the numerous RDTs available have limitations. A closer look at the methods for infection, replication, and reproduction of major pathogens in Fig. 2 may shed light on the opportunity—and challenge—of identifying effective biomarkers that can be used for development of diagnostic tests.

A. Rapid Lateral Flow Immunoassays

The first RDTs, with principles of latex agglutination and radioimmunoassay, were developed in the 1950s and 1960s; RDT technology matured to the point of wide commercialization in the 1980s. Today, RDTs for global infectious diseases are supplied by more than 200 manufacturers worldwide, in the form of dipsticks, cards, cassettes, strip tests, or pads, and are generally easy-to-use and inexpensive ($1–$10 per test result). The most familiar RDT is the home pregnancy test; in global health, the HIV antibody test and the malaria RDT are the most widely used, each performed at least 100 million times per year worldwide [8], [9].

Despite their tremendous impact, lateral flow RDTs have fundamental limitations. First, the level of detection is limited to proteins present in high molar concentrations, like antibodies produced in response to chronic viral infections. For instance, malaria RDTs that target the malarial proteins pLDH (Parasite lactate dehydrogenase) or PfHRP2 (Histidine-rich protein 2 of *P. falciparum*) can reliably detect malaria only when at least 200 pfu/ml are present in the blood, a relatively large infectious burden. As a result, malaria RDTs will misdiagnose most patients with low-level parasitemia. While many of these patients are minimally symptomatic, they remain sources of malaria transmission. Thus, while malaria RDTs remain extremely useful *clinically*, they are not sensitive enough to support public health programs designed to stop malaria transmission or eliminate malaria entirely—which would

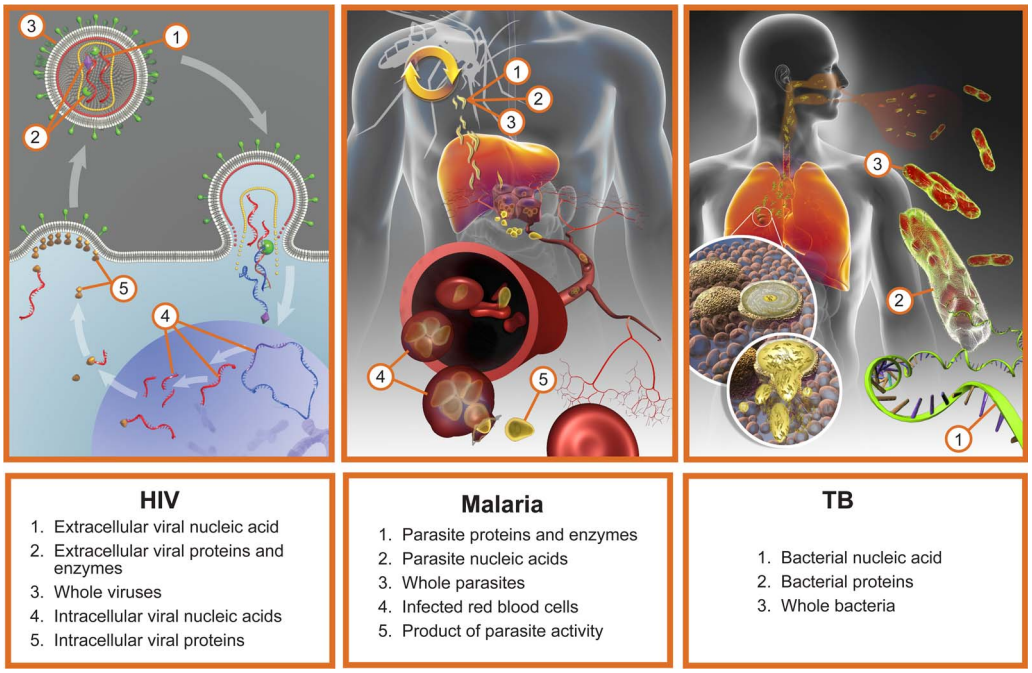

Fig. 2. ***Methods of infection, replication, and production of HIV, malaria and TB. An understanding of the underlying mechanisms of pathogen replication and activity reveals specific biomarkers that may be leveraged for diagnostic purposes.***

require diagnosis and treatment of asymptomatic carriers not currently detectable by RDTs.

Second, lateral flow RDTs are not generally applicable to conditions in which a biomarker does not exist in high concentrations in body fluids. For these conditions, so-called "molecular tests," which can measure protein antigens, RNA, and/or DNA derived from the pathogens themselves, are required. In particular, "viral loads" in the form of viral protein antigen or viral nucleic acid tests for HIV, hepatitis B virus (HBV), hepatitis C virus (HCV), influenza, and dengue have proven to be essential to accurately diagnose these conditions. In addition to the fact that the target biomarkers are present at low molar concentrations, they often are tucked away inside cells, or complexed—meaning, hidden—within agglomerations of host proteins. The challenge of isolating the target molecule for subsequent detection—a fluid processing challenge ill-suited to RDTs—represents the thorny problem of sample preparation.

B. State-of-the-Art Technologies: NAT and Cell Counting

Broadly speaking, the state-of-the-art in infectious disease diagnostics is nucleic acid testing (NAT). NAT is sensitive and can allow for the detection and even quantification of just a few pathogens in a body fluid (e.g., blood plasma and sputum) by amplifying the RNA or DNA sequences that are uniquely contained within the infectious organism. NAT is necessary for the most accurate quantitative assessment of viral loads and drug resistance testing. The challenge for global health applications, however, is that NAT typically involves large instruments, expensive reagents, and trained operators; therefore, functioning NAT systems are rarely found in developing countries, even in large hospitals and universities.

A few technologies, however, have emerged to increase the availability of NAT, although still not portable or hand-held. The Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, CA), for example, was endorsed by the World Health Organization (WHO) in 2011 [10], [11]. Operated on Cepheid's GeneXpert platform, GeneXpert MTB/RIF performs real-time PCR (Polymerase chain reaction) to detect *M. tuberculosis* identification at concentrations as low as 131 cfu/ml as well as genetic mutations responsible for 99.5% of rifampicin resistant strains [10]. Reflecting the major gap in the diagnostics portfolio that the GeneXpert has begun to address, more than 3700 GeneXpert instruments and more than 10 million GeneXpert MTB/RIF cartridges have been procured as of December 31, 2014 in the public sector in 116 of 145 countries eligible for concessional pricing pursuant to the TBXpert Project, a three-year UNITAID-funded collaboration executed by the WHO Global TB Programme and the Stop TB Partnership secretariat [12]. As a result of the Programme, individual tests and the instrument itself have been made available to high-burden developing countries at $9.98 and $17 000.00, respectively [13]. The GeneXpert has been a significant step forward in decentralizing TB testing, but because of the technical requirements for the test, including the need for phlebotomy and electricity, as well as the lack of portability of the platform, it cannot be used at the lowest levels of the healthcare system in resource-limited settings. A point-of-care, hand-held NAT using a finger prick or submilliliter volumes is still a technical grand challenge not met, although miniature devices claiming to accomplish this feat are beginning to appear [14].

In addition to NAT, cell counting is a major need in global infectious diseases diagnostics. In particular, the CD4+ T lymphocyte count is critical to the management of HIV disease and the staging of patients infected with HIV. Typically assessed by flow cytometry, the instrumentation for CD4 counting suffers from the same practical limitations as standard NAT systems. However, increasingly portable cell counting technologies like the Pima CD4 Test (Alere Inc., Waltham, MA) have emerged. The Pima CD4 Test requires 25 μl of whole blood—volume that can be obtained from a finger prick with no need for venipuncture—and it became the first point-of-care CD4 assay to make the list of WHO prequalified diagnostics when it was added in 2012 [15]. Several companies have followed suit with comparable CD4 technologies, including BD's FACSPresto, and products from Daktari Diagnostics and Omega Diagnostics [15].

C. The Role of Micro- and Nanotechnologies

Broadly stated, the challenge in accurate diagnosis can be divided into performing two processes, *sample preparation* and *target detection*, simply, quickly, accurately, and inexpensively. Sample preparation is the less glamorous and more challenging problem. Body fluids, especially blood and sputum, are complex, and generally filled with a significant amount of cells, proteins, DNA, and small molecules other than the target biomarker which, from a diagnostic perspective, represent "noise," or background signals that have to be overcome. The first step in diagnostic testing is to remove as much of this noise as possible, while retaining the target of interest. In sophisticated laboratories, this is addressed by repetitive steps of filtering and washing the sample in a variety of buffers and chemicals using manual or robotic pipetting techniques. Miniaturizing sample preparation protocols has proven to be a tremendous challenge for most diagnostic technologies.

Once the target signal has been washed and purified (and in the case of nucleic acids, amplified), the second step is detection. A wide variety of techniques have been developed to detect biological signals at the micro and nanoscale. These include optical sensing methods, ranging from color changes visible to the human eye to single-molecule fluorescence sensors, as well as electrochemical, electromagnetic and mass sensors. Each detection technique has unique advantages and weaknesses; the best serve as general detection platforms applicable to a

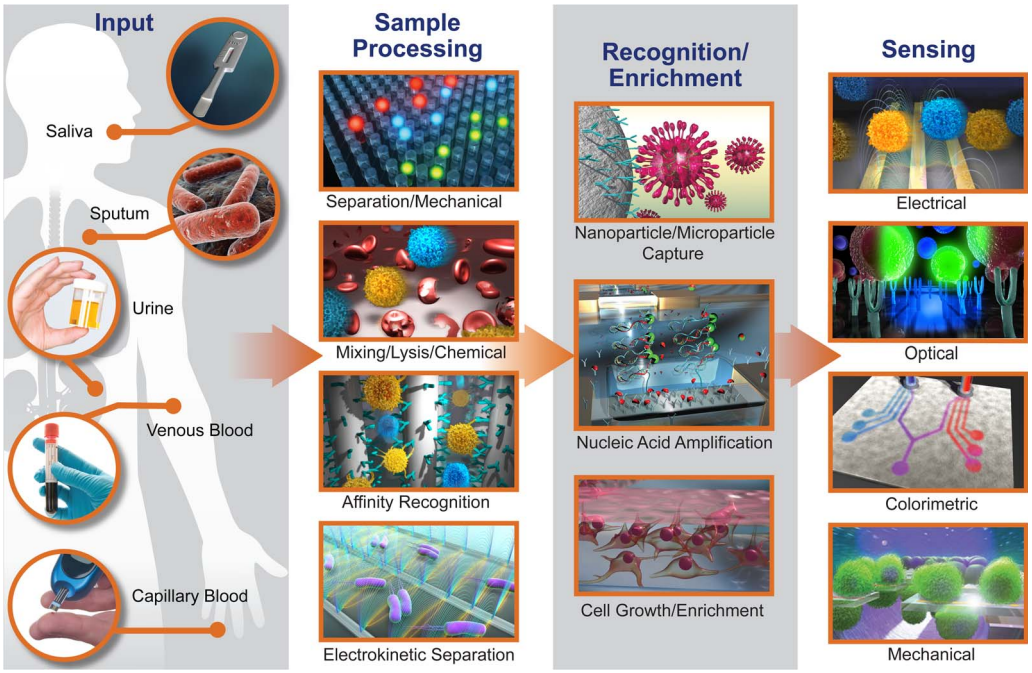

Fig. 3. ***A broad overview of micro- and nanoscale technologies that can be applied to common body fluid samples to address the two challenges of point-of-care diagnostics: sample processing and sensing.***

variety of biomarkers and infectious disease pathogens. For global health applications, successful detection techniques need to be exquisitely simple, easy to miniaturize, or both.

Collectively, efforts to develop point-of-care systems that can process body fluids, and isolate and detect infectious pathogens or their physiologic signatures at small scale, have coalesced under the broad headings of *microfluidics* and *nanotechnology*. Fig. 3 summarizes the broad categories under which most of these techniques fall.

IV. MICROFLUIDIC SAMPLE PREPARATION

The diverse collection of microfluidic sample preparation approaches include **mechanical**, **magnetic**, **electrokinetic**, **immunoaffinity**, and **chemical** techniques. The appropriate choice of approach, or combination of approaches, is determined by the sample source and the analyte of interest. Sputum, whole blood, and other biological fluid samples each exhibit their own set of challenges for microfluidic sample preparation. Sputum is highly viscous and hard to obtain in large volumes, while a few microliters of blood contain millions of cells that have inherent clotting tendencies.

Detecting blood-borne pathogens such as HIV and HCV, bacteria in sputum, or even a single blood cell subtype requires isolating the target and/or clearing a sample of contamination. Detection of viruses from whole blood may require the extraction of blood plasma due to the small size and quantity of viruses compared to cells. Traditionally, whole blood is processed in large volumes (several milliliters) by centrifugation, chemical lysis, or immunoaffinity isolation kits. While microfluidic methods can draw on the basic principles of these laboratory methods, they also offer some opportunities available only at the micro scale.

A. Physical Filtration

Physical filtration in microfluidic sample processing takes advantage of the sizes of sample components to separate cells or contaminants. Microfluidic filters can employ arrays of pillars, porous membranes, or micron-sized holes, and can be useful for size separation, although they are very susceptible to clogging, especially with blood samples [16]–[21]. As an example, in a flow-through immunoassay capable of detecting 20 ng/ml of pfHRPII, a plasma extraction membrane is used to separate malaria protein from larger blood components [21].

B. Hydrodynamic Methods

Hydrodynamic methods leverage laminar flow—a characteristic behavior of fluids at a small scale—and the forces on sample components in precisely designed fluidic channels with carefully controlled flow rates, usually to focus cells within a sample or to enrich the target by removing as many contaminants as possible [16], [19], [22], [23]. For example, *deterministic lateral displacement* employs an array of pillars to separate large cells from a blood

sample, and is capable of removing nearly 100% of lymphocytes and monocytes, though the flow rate is slow, only 1 μl min^{-1} [16]. Another recent example adds to the deterministic lateral displacement method with hydrodynamic focusing that enables sorting rare tumor cells by magnetophoresis and is capable of processing 8ml hour^{-1} [24]. These techniques are promising, though the repeatability of precise geometries and flow rates—typically controlled by laboratory syringe pumps—is yet to be demonstrated on a mass-production scale.

On the other hand, some microfluidic techniques aim to mix samples with other reagents, often employing channel designs to induce turbulent flow. Several examples have emerged that leverage osmotic forces and precise timing to selectively lyse erythrocytes [25]–[27]. In one study to separate white blood cells from red blood cells, for example, a serpentine microfluidic channel patterned with herringbone structures was used to rapidly mix blood at 20 μl min^{-1} with hypotonic solution and lyse erythrocytes before restoring osmolarity by mixing a second buffer, thus preserving white blood cells which remain largely intact through the brief exposure to hypotonic solution [25]. This approach appears to be an effective method for quickly processing whole blood leading to white blood cell measurements, though it once again relies on precise timing, and to the knowledge of the authors, has not yet been adapted for commercial production.

C. Immunoaffinity Techniques

Immunoaffinity techniques are widely employed in microfluidic sample processing when an antibody with specificity for the target is available. Surface chromatography in which an antibody is immobilized on one or more planes of a microfluidic device have been used for applications, including isolating CD4+ T cells [26], [28], [29], and even whole viruses [30] from blood. A recent report of CD4+ T cell capture demonstrated up to 98.3% efficiency [26], while a report of microfluidic capture of viruses on a planar surface reported between 60% and 80% capture for different virus subtypes [30]. In a more common approach, micro- or nanoparticles, particularly magnetic particles, functionalized with antibodies are mixed with the sample to bind the analyte and then separated downstream. Recent work demonstrates magnetic particle binding capable of separating 78% of HIV virions from blood plasma [31], and detecting HIV capsid protein p24 as low as 0.1 pg/ml as part of a biobarcode detection system [32], among others.

While immunoaffinity is the basis of separation or recognition components of several established technologies, it can be challenging—antibodies may be the most expensive component of many point-of-care diagnostics. Other recognition elements may be employed as well, such as nucleic acid aptamers specifically designed to bind a target and DNA strands complementary to a sequence of interest. While the cost of aptamers still remains very high, one recent example employs polymer beads and magnetic nanoparticles functionalized with DNA for capture and labelling of nucleic acid from TB, enabling detection of as low as 10^3 bacteria from 1 ml of sputum with a micro-NMR (Nuclear Magnetic Resonance) barcode sensing method [33].

Microfluidic devices can also be fabricated with electrodes in order to implement **electrokinetic methods** in the enrichment or concentration of a target in a biological sample. Electrophoresis, the migration of cells or molecules in an externally applied magnetic field, has been applied in microfluidic systems but has limited throughput and may require high voltages [20]. Dielectrophoresis, on the other hand, employs an alternating current (AC) electric field which polarizes particles, resulting in a net force either in the direction or opposite the direction of the electric field. This technique has been reported and applied widely to cells and micro- and nanoparticles, and can be used to concentrate a target in a microfluidic system—in one example, dielectrophoresis was employed in a microfluidic device, resulting in 50- to 200-fold enrichment of malaria-parasitized cells [34]. However, this technique has not yet translated to commercial applications, largely because the forces are very weak in high salt physiologic solutions, while the use of low ionic strength solutions is rather prohibitive in practical applications. In the unique case of red blood cells, which are susceptible to magnetic forces, magnetism has also been used for sample processing in microfluidic devices, though the results do not suggest this method is suitable for highly-efficient separation of erythrocytes [20], [35].

In the end, the primary goal of microfluidic sample processing techniques like those described above is to enable increased detection sensitivity while keeping input sample volumes low. When coupled with the sensing technologies described below, microfluidics may be able to address many of the pitfalls of currently available technologies: for instance, RDTs which require high molar concentrations of analytes, or other point-of-care diagnostic systems that still require manual sample processing steps and are not fully automated, sample-to-answer capable.

V. MICRO- AND NANOSCALE DETECTION TECHNOLOGIES

The ideal detection approach for global health applications for diagnostics should be low-cost, easy-to-use and robust technologies that are as sensitive as those employed in state-of-the-art laboratory instruments. Micro- and nanotechnologies offer a variety of solutions, each with its own advantages and drawbacks. While a major drawback of optical detection methods in point-of-care diagnostics for resource-limited settings has been the cost and size of lasers, photodetectors and cameras, the latest trend in camera technologies promises to put increasingly capable imaging ability into smartphones, which are already being used for diagnostics applications. Nonoptical methods, particularly electrical impedance sensing, are attractive for

their simplicity. As discussed here, a number of approaches aim at miniaturizing PCR, flow cytometry, and even microscopy, with micro- and nanoscale technologies, while others leverage submicron fabrication techniques to create novel sensing modalities.

A. Optical Methods

Common optical detection methods include **fluorescence**, **absorbance**, and **chemiluminescence** [36]. **Fluorescence** is highly sensitive and perhaps the most common optical technique in diagnostics, widely employed in microscopy, flow cytometry, and molecular biology measurements like PCR. Fluorescent markers conjugated to antibodies for proteins or other cellular components give this approach an excellent specificity. Many micro-scale technologies have employed fluorescence detection, often incorporating a laser or LED (light-emitting diode) for excitation of the tag.

Fluorescence microscopy has for a long time been a standard method for TB detection in sputum samples, but has been difficult to implement in the field. Although recently LED-based microscopy has increased access to microscopy [37], it is still limited by lack of portability and the need for a trained technician. In one microscale technique employing fluorescence for whole-cell TB detection, bacteria from a processed sputum sample are concentrated, captured, and tagged on the surface of a microtip, which is then imaged with a camera, demonstrating a lower limit of detection of 200 CFU ml^{-1} from spiked sputum and 10 CFU ml^{-1} in buffer [38]. In another approach, antibody-conjugated magnetic beads are used to separate bacteria from a sample and quantum dots are used as labels for detection, demonstrating sensitivity down to 10^3 bacteria ml^{-1} when a spectrofluorometer is used [39].

In addition to imaging approaches, fluorescence is commonly used as an indicator in NAT, either as a DNA intercalating dye or as part of a fluorophore-quencher system conjugated to probe DNA. Numerous nucleic acid amplification on-a-chip approaches incorporate similar methods, including the digital SlipChip device capable of detecting 37 copies/ml of viral RNA with HIV and HCV samples [40]. Many NATs include isothermal alternatives like Loop-Mediated Isothermal Amplification (LAMP), which are common in micro- and nanotechnology approaches, though it remains to be seen whether a test can be made sufficiently low-cost and robust for use in a handheld, ultra-portable device that could improve upon the capabilities of systems like the GeneXpert.

Unlike fluorescence, the appeal of absorbance approaches like **colorimetry** is that the signal is visible to the naked eye, which can eliminate the need for cameras in tests where a qualitative result is desired. Among the drawbacks is that instrument-based analysis of colorimetric signals is not as precise as other methods. Gold nanoparticles are a common component of colorimetric tests for the color-change phenomenon observed when they are concentrated. The previously-mentioned example employing a membrane filter and capable of detecting 20 ng/ml of pfHRPII uses antibody-conjugated gold nanoparticles for colorimetric detection, with quantitative analysis achieved by reading the result with a flatbed scanner [21]. An example of a nanoparticle-based TB detection strategy is one that employs gold nanoparticles attached to short strands of DNA that are complementary to opposite ends of a target amplicon and produce a visible color change when 0.75 μg or more of DNA is present [41]–[43]. Subsequent reports describe versions of the approach on a portable platform [42] and on paper substrates [43].

Chemiluminescence, the emission of light from a chemical reaction, is also a useful approach for portable diagnostics as it does not require an external light source, though it is limited by the reagents available to produce such a signal [36]. An example is an ELISA-style CD4-counting approach in which CD4 T cells are first separated with antibody-conjugated magnetic beads, tagged with another antibody conjugated to horseradish peroxidase, and the signal measured with a cell phone camera [44]. CD4 counts determined by this method showed an 0.86 R^2 compared to flow cytometry for HIV patients with CD4 counts between 237 and 1446 cells μl^{-1} [44]. Although this is an interesting approach that leverages a standard mobile phone device, the need for multiple antibodies limits its ability to be low cost.

Other optical detection technologies include the lens-less shadow imaging technique in which diffraction patterns are imaged by a detector behind an illuminated sample. Shadow imaging has been employed for whole cell detection in microfluidic devices, including for point-of-care testing of CD4+ count [45], [46]. Additionally, plasmon resonance has been employed to detect the binding of intact viruses on a gold nanoparticle surface functionalized with antibodies down to 98 +/−39 virus copies/ml in the best report [47]. Another report from the same group employed photonic crystals to detect viruses from spiked plasma between 10^4 and 10^8 copies/ml [48].

B. Nonoptical Methods

Non-optical methods exhibit a different set of advantages and drawbacks. **Electrical sensing techniques** are often simpler and cheaper than optical methods; however, they typically rely heavily on sample processing steps to remove background noise. Impedance spectroscopy measures electrical impedance of an aqueous solution as a function of AC frequency, commonly using microfabricated electrodes. The presence of a cell-sized target obstructing the movement of charge carrying ions in the solution, or changes in ion concentration as a result of cell lysis, or metabolism have been used as the basis for sensors measuring a variety of targets including cells and small molecules.

One technology counts CD4+ T cells after immunoffinity separation from whole blood by a method called lysate impedance spectroscopy, which measures impedance

change resulting from the release of intracellular ions and is capable of detecting 20 cells μl^{-1} [28]. Another is a microfabricated Coulter counter with dual-frequency impedance sensing capable of distinguishing white blood cell populations, and enumerating CD4+ T cells with the addition of a bead attached to the CD4 surface marker, demonstrating 95% correlation with clinical laboratory equipment [49]. A third example draws on both approaches to count CD4 and CD8 T cell cells from whole blood in a differential counting approach in which cells are counted before and after immunoaffinity depletion in a microfluidic chamber, demonstrating an R^2 of 0.92 for CD4 counts compared to a clinical laboratory's standard [26]. Similar impedance-based cell counting approaches have also been used to distinguish the intrerythrocytic stages of malaria-infected red blood cells, as well as to distinguish infected from uninfected cells [50], [51]. In our view, the impedance-sensing approach to cell counting is a highly promising approach, and it is already emerging in commercial applications.

Another electrical detection method, voltammetry, measures the current in a sample as a response to varied electrical potential. One example detects IFN-γ (Interferon gamma)s released in the presence of TB antigens, an indicator of latent TB infection, by voltammetry employing micro-patterned half-ring electrodes as the detector component which surround a site for cell attachment, capable of detecting IFN-γ at concentrations between 0.06 and 10 nM [52], [53].

Electrochemical approaches are similarly promising, though they are limited to enzymes and reagents capable of producing an electrochemical signal. One method sandwiches pfHRPII from spiked human serum between two antibodies, one covalently linked to a magnetic nanoparticle and the other bound to a reporter enzyme, horseradish peroxidase [54]. The sandwiches are then drawn magnetically to the surface of an electrode, which is polarized by the enzyme-facilitated chemical reactions, enabling detection of pfHRPII at concentrations as low as 0.36 $ngml^{-1}$ [54]. There is some question, however, whether an approach like this provides any advantage over a traditional ELISA as it requires many of the same reagents.

Other approaches may detect **mass or mechanical forces**. For example, a piezoelectric immunosensor designed to bind pfHRPII in diluted human serum could detect mass changes as a shift in the resonant frequency of an antibody-functionalized quartz crystal microbalance, facilitating detection down to 12 ng ml^{-1} [55]. However, as is true with many mechanical sensors, there is some concern whether such a sensor exhibits the robustness necessary for a hand-held diagnostic test. Nevertheless, one example which appears promising for its simplicity is a microfluidic system in which red blood cells are passed through a funnel chain with micron-sized constrictions measuring the threshold deformation pressure required to squeeze the cell through, finding that parasitized cells are between 1.5 and 200$\times$ stiffer than healthy red blood cells [56]. It is suggested that this microfluidic approach can be used for detection of the presence of malaria parasites and assessment of treatment efficacy, although there is a question as to whether the throughput would be sufficient to process enough sample in a short time.

But innovations in micro and nanotechnology do not appear to be only within the categories mentioned here. As microfabrication techniques improve, we may find sophisticated measurement techniques increasingly miniaturized for diagnostic applications, and we may be seeing glimpses of this already. For example, consider the previously mentioned report in which amplified DNA from TB was detected with micro NMR [33]. Additionally, mass spectrometry, a highly sensitive technique for measuring the composition of materials based on charge and molecular weight, has been miniaturized and coupled with microfluidic devices [57], and may be among the next generation of detection methods to be adapted for the point-of-care.

It is one thing to demonstrate the enrichment of an analyte from a biological sample, and another to show the sensitive detection of analyte in a debris-free buffer or after the sample has been processed by standard laboratory methods. The integration of these pieces, however, presents a new challenge. The quest for complete sample-to-answer platforms requires coping with the added complexity of loading and metering the biological sample, and tuning microfluidic devices, flow rates, and capillary forces. These are problems often barely examined in research laboratories, but inevitably faced when moving from prototyped devices to plastics and mass manufacturing.

VI. RESEARCH FUNDING AND COMMERCIALIZATION OF MICRO- AND NANOTECHNOLOGY DIAGNOSTICS

The road from discovery to delivery of diagnostic products involves many steps, and the process can easily take five years or more, even after prototype development, and costs can run from $5 million to $50 million or more. Funding is frequently an early barrier to product development, and can slow the process even more than technical challenges. Mobilizing funding for diagnostic products designed for the developing world is particularly difficult, as financial returns on such products are generally expected to be low relative to products being developed for resource-rich settings.

Seed funding for basic research and proof-of-principle of a new diagnostic technology, including platform development and feasibility studies, is often available from a variety of sources, including the National Science Foundation (NSF), the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), the Bill & Melinda Gates Foundation, and Small Business Innovation Research (SBIR) grants. In the next stage of product development, including prototype development, clinical trials and product optimization, funding

may be available from angel investors, technology laboratories and SBIR Phase II grants, among others. However, at the subsequent stage of product development, including pre-market validation, manufacturing scale-up, and commercial release and regulatory approval, funding for new diagnostics is very difficult to obtain, and has often been called the 'valley of death' facing new product concepts and start-up companies. Possible sources of funding include venture capital, corporate venture funds, and commercial debt. Some funders, including UNITAID, Children's Investment Fund Foundation, and others may provide funding at the later stages of product development, but only for certain targeted disease areas (e.g., TB, HIV, malaria) or target populations (children).

With respect to microfluidics and nanotechnologies for detection of global infectious diseases, many of which are in the earliest stages of development, additional governmental and nongovernmental funding sources are needed to accelerate their path from bench to bedside. Moreover, from the point of design lockdown through market validation and manufacturing scale-up, additional sources of funding and new business models to facilitate commercialization and uptake of new diagnostic technologies are sorely needed. The business model for commercializing point-of-care devices for global health infectious diseases is unique. The entities purchasing these devices are typically governments of high-burden countries, often using international aid from developed countries and foundations. Meanwhile, manufacturing technologies from the developed world lead to individual tests that are too costly to be sold in the developing world, unless a sufficient volume of demand measured in the millions of units can make the price point financially attractive.

VII. OUTLOOK

Micro- and nanotechnologies have enabled clear progress in HIV diagnostics, with the commercial availability of microfluidics-based CD4+ T cell counting using a drop of blood from a finger prick. The next grand challenge in HIV diagnostics is to reliably measure viral load from a drop of blood at the point-of-care with high sensitivity. Methods based on capture and detection of whole virus particles, may be simpler to implement but less sensitive than approaches involving nucleic acid amplification-based methods. A point-of-care, single-use nucleic acid-based detection of viruses from a finger prick is a technical challenge that still needs to be addressed. In fact, management of TB, malaria, and a host of other infectious diseases would benefit from such a point-of-care, single-use nucleic acid amplification device.

Mobile health care is a trend that is here to stay. Improvements in camera technology allow for unprecedented levels of sensitivity and spatial resolution for detection of optical signals. The use of sensors and adaptors with smartphone cameras and other mobile technologies is likely to increase dramatically. In additional to cell phone-based optical approaches, electronic or electrochemical approaches based on impedance or field effect mechanisms can provide direct interface between the system and the sensors resulting in portable and miniaturized devices.

It should also be noted that as the cost of sequencing continues to approach $1000 and lower, the full sequencing of genomes of pathogens may be an option that is not far off, providing holistic analysis of a pathogen as well as aiding in the identification of new and unknown strains and mutants. Unconventional approaches such as portable mass spectrometers coupled with microfluidic sample preparation approaches could allow for determination of peptides, protein fragments and related biomarkers to identify pathogens using fingerprinting and data analytics. However, whether desired sensitivities from small samples can be achieved is an open question.

While the progress in research and feasibility demonstrations of micro- and nanotechnology-based diagnostics for HIV, TB, and malaria have been rapid, the commercialization and translation is only beginning to become a reality. Challenges still include the cost of manufacturing, production and scale up itself and the corresponding business models for financial success. Continued philanthropic sources and funding from the developed world would be critically needed to sustain further investments for commercialization of the promising approaches. The potential for impact is limitless as millions of people can benefit if these technologies can be commercialized and brought into the hands of the health care providers in the world's poorest regions that are disproportionately impacted by these infectious diseases. ■

REFERENCES

[1] United Nations, "The millennium development goals report 2014," New York, NY, USA, 2014.

[2] W. H. Organization, "Global tuberculosis report 2013," Geneva, Switzerland, 2013.

[3] World Health Organization, "World health statistics 2014," 2014.

[4] World Health Organization, "Roll back Malaria partnership: A decade of partnership and results," Geneva, Switzerland, 2011.

[5] A. N. Abou Tayoun, P. R. Burchard, I. Malik, A. Scherer, and G. J. Tsongalis, "Democratizing molecular diagnostics for the developing world," *Amer. J. Clin. Pathol.*, vol. 141, no. 1, pp. 17–24, Jan. 2014.

[6] RAND Corporation, "Estimating the global health impact of improved diagnostic tools for the developing world," 2007.

[7] C. F. Rowley, "Developments in CD4 and viral load monitoring in resource-limited settings," *Clin. Infect. Dis.*, vol. 58, no. 3, pp. 407–412, Mar. 2014.

[8] World Health Organization, "Malaria World Report 2013," World Health Organization, Aug. 2013.

[9] World Health Organization, "Global health observatory (GHO): HIV/AIDS," 2012. [Online]. Available: http://www.who.int/gho/hiv/en/

[10] W. H. Organization, "Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and Rifampicin resistance: Xpert MTB/RIF," 2011.

[11] K. Dheda, M. Ruhwald, G. Theron, J. Peter, and W. C. Yam, "Point-of-care diagnosis of tuberculosis: Past, present and future," *Respirology*, vol. 18, no. 2, pp. 217–232, Mar. 2013.

[12] World Health Organization, "TB diagnostics and laboratory strengthening," 2014, [Accessed: 22-Feb-2015]. [Online]. Available:

http://who.int/tb/laboratory/mtbrifrollout/en/

[13] Foundation for Innovative New Diagnostics, "Price for Xpert MTB/RIF and FIND country list," 2013, [Accessed: 08-Dec-2014]. [Online]. Available: http://www.finddiagnostics.org/about/what_we_do/successes/find-negotiated-prices/xpert_mtb_rif.html

[14] C. Toumazou, L. M. Shepherd, S. C. Reed, G. I. Chen, A. Patel, D. M. Garner, C.-J. Wang, C.-P. Ou, K. Amin-Desai, P. Athanasiou, H. Bai, I. M. Q. Brizido, B. Caldwell, D. Coomber-Alford, P. Georgiou, K. S. Jordan, J. C. Joyce, M. La Mura, D. Morley, S. Sathyavruthan, S. Temelso, R. E. Thomas, and L. Zhang, "Simultaneous DNA amplification and detection using a pH-sensing semiconductor system," *Nat. Methods*, vol. 11, pp. 1–8, Jun. 2013.

[15] M. T. Glynn, D. J. Kinahan, and J. Ducrée, "CD4 counting technologies for HIV therapy monitoring in resource-poor settings—State-of-the-art and emerging microtechnologies," *Lab Chip*, vol. 13, no. 14, pp. 2731–2748, Jul. 2013.

[16] J. Davis, D. W. Inglis, K. J. Morton, D. Lawrence, L. R. Huang, S. Y. Chou, J. C. Sturm, and R. H. Austin, "Deterministic hydrodynamics: Taking blood apart," *PNAS*, vol. 103, no. 40, pp. 14779–14784, Oct. 2006.

[17] S. Nagrath, L. V Sequist, S. Maheswaran, D. W. Bell, D. Irimia, L. Ulkus, M. R. Smith, E. L. Kwak, S. Digumarthy, A. Muzikansky, P. Ryan, U. J. Balis, R. G. Tompkins, D. Haber, and M. Toner, "Isolation of rare circulating tumour cells in cancer patients by microchip technology," *Nature*, vol. 450, no. 7173, pp. 1235–1239, Dec. 2007.

[18] C. Liu, M. Mauk, R. Gross, F. D. Bushman, P. H. Edelstein, R. G. Collman, and H. H. Bau, "Membrane-based, sedimentation-assisted plasma separator for point-of-care applications," *Anal. Chem.*, vol. 85, no. 21, pp. 10463–10470, Nov. 2013.

[19] Z. T. F. Yu, K. M. Aw Yong, and J. Fu, "Microfluidic blood cell sorting: Now and beyond," *Small*, vol. 10, no. 9, pp. 1687–1703, May 2014.

[20] W. Tian and E. Finehout, "Microfluidic diagnostic systems for the rapid detection and quantification of pathogens," *Microfluid. Biol. Appl.*, pp. 1–52, 2009.

[21] L. Lafleur, D. Stevens, K. McKenzie, S. Ramachandran, P. Spicar-Mihalic, M. Singhal, A. Arjyal, J. Osborn, P. Kauffman, P. Yager, and B. Lutz, "Progress toward multiplexed sample-to-result detection in low resource settings using microfluidic immunoassay cards," *Lab Chip*, vol. 12, no. 6, pp. 1119–1127, Mar. 2012.

[22] N. Watkins, B. M. Venkatesan, M. Toner, W. Rodriguez, and R. Bashir, "A robust electrical microcytometer with 3-dimensional hydrofocusing," *Lab Chip*, vol. 9, no. 22, pp. 3177–3184, Nov. 2009.

[23] S. Yang, A. Undar, and J. D. Zahn, "A microfluidic device for continuous, real time blood plasma separation," *Lab Chip*, vol. 6, no. 7, pp. 871–880, Jul. 2006.

[24] E. Ozkumur, A. M. Shah, J. C. Ciciliano, B. L. Emmink, D. T. Miyamoto, E. Brachtel, M. Yu, P. Chen, B. Morgan, J. Trautwein, A. Kimura, S. Sengupta, S. L. Stott, N. M. Karabacak, T. a Barber, J. R. Walsh, K. Smith, P. S. Spuhler, J. P. Sullivan, R. J. Lee, D. T. Ting, X. Luo, A. T. Shaw, A. Bardia, L. Sequist, D. N. Louis, S. Maheswaran, R. Kapur, D. a Haber, and M. Toner, "Inertial focusing for tumor antigen-dependent and-independent sorting of rare circulating tumor cells," *Sci. Transl. Med.*, vol. 5, no. 179, p. 179ra47, Apr. 2013.

[25] P. Sethu, L. L. Moldawer, M. N. Mindrinos, P. O. Scumpia, C. L. Tannahill, J. Wilhelmy, P. Efron, B. H. Brownstein, R. G. Tompkins, and M. Toner, "Microfluidic isolation of leukocytes from whole blood for phenotype and gene expression analysis," *Anal. Chem.*, vol. 78, no. 15, pp. 5453–5461, Aug. 2006.

[26] N. N. Watkins, U. Hassan, G. Damhorst, H. Ni, A. Vaid, W. Rodriguez, and R. Bashir, "Microfluidic CD4+ and CD8+ T Lymphocyte Counters for Point-of-Care HIV Diagnostics Using Whole Blood," *Sci. Transl. Med.*, vol. 5, no. 214, p. 214ra170, Dec. 2013.

[27] P. Sethu, M. Anahtar, L. L. Moldawer, R. G. Tompkins, and M. Toner, "Continuous flow microfluidic device for rapid erythrocyte analysis," *Anal. Chem.*, vol. 76, no. 21, pp. 6247–6253, Nov. 2004.

[28] X. Cheng, Y. Liu, D. Irimia, U. Demirci, L. Yang, L. Zamir, W. R. Rodríguez, M. Toner, and R. Bashir, "Cell detection and counting through cell lysate impedance spectroscopy in microfluidic devices," *Lab Chip*, vol. 7, no. 6, pp. 746–755, Jun. 2007.

[29] N. N. Watkins, S. Sridhar, X. Cheng, G. D. Chen, M. Toner, W. Rodriguez, and R. Bashir, "A microfabricated electrical differential counter for the selective enumeration of CD4+ T lymphocytes," *Lab Chip*, vol. 11, no. 8, pp. 1437–1447, Apr. 2011.

[30] S. Wang, M. Esfahani, U. Gurkan, F. Inci, D. R. Kuritzkes, and U. Demirci, "Efficient on-chip isolation of HIV subtypes," *Lab Chip*, vol. 12, no. 8, pp. 1508–1515, Mar. 2012.

[31] G. Chen, C. J. Alberts, W. Rodriguez, and M. Toner, "Concentration and purification of human immunodeficiency virus type 1 virions by microfluidic separation of superparamagnetic nanoparticles," *Anal. Chem.*, vol. 82, no. 2, pp. 723–728, Jan. 2010.

[32] E. Kim, J. Stanton, and B. Korber, "Detection of HIV-1 p24 Gag in plasma by a nanoparticle-based bio-barcode-amplification method," *Nanomedicine*, vol. 3, no. 3, 2008.

[33] M. Liong, A. N. Hoang, J. Chung, N. Gural, C. B. Ford, C. Min, R. R. Shah, R. Ahmad, M. Fernandez-Suarez, S. M. Fortune, M. Toner, H. Lee, and R. Weissleder, "Magnetic barcode assay for genetic detection of pathogens," *Nat. Commun.*, vol. 4, p. 1752, Jan. 2013.

[34] P. Gascoyne, C. Mahidol, M. Ruchirawat, J. Satayavivad, P. Watcharasit, and F. F. Becker, "Microsample preparation by dielectrophoresis: Isolation of malaria," *Lab Chip*, vol. 2, no. 2, pp. 70–75, May 2002.

[35] K.-H. Han and A. Bruno Frazier, "Continuous magnetophoretic separation of blood cells in microdevice format," *J. Appl. Phys.*, vol. 96, no. 10, p. 5797, 2004.

[36] B. Kuswandi, N. J. Huskens, and W. Verboom, "Optical sensing systems for microfluidic devices: A review," *Anal. Chim. Acta*, vol. 601, no. 2, pp. 141–155, Oct. 2007.

[37] W. H. Organization, Fluorescent light-emitting diode (LED) microscopy for diagnosis of tuberculosis: Policy statement," 2011.

[38] J.-H. Kim, W.-H. Yeo, Z. Shu, S. D. Soelberg, S. Inoue, D. Kalyanasundaram, J. Ludwig, C. E. Furlong, J. J. Riley, K. M. Weigel, G. Cangelosi, K. Oh, K.-H. Lee, D. Gao, and J.-H. Chung, "Immunosensor towards low-cost, rapid diagnosis of tuberculosis," *Lab Chip*, vol. 12, no. 8, pp. 1437–1440, Apr. 2012.

[39] E. Liandris, M. Gazouli, M. Andreadou, L. a Sechi, V. Rosu, and J. Ikonomopoulos, "Detection of pathogenic mycobacteria based on functionalized quantum dots coupled with immunomagnetic separation," *PLoS One*, vol. 6, no. 5, p. e20026, Jan. 2011.

[40] F. Shen, B. Sun, J. E. Kreutz, E. K. Davydova, W. Du, P. L. Reddy, L. J. Joseph, and R. F. Ismagilov, "Multiplexed quantification of nucleic acids with large dynamic range using multivolume digital RT-PCR on a rotational SlipChip tested with HIV and hepatitis C viral load," *J. Amer. Chem. Soc.*, vol. 133, no. 44, pp. 17705–17712, Nov. 2011.

[41] P. V Baptista, M. Koziol-Montewka, J. Paluch-Oles, G. Doria, and R. Franco, "Gold-nanoparticle-probe-based assay for rapid and direct detection of Mycobacterium tuberculosis DNA in clinical samples," *Clin. Chem.*, vol. 52, no. 7, pp. 1433–1434, Jul. 2006.

[42] L. B. Silva, B. Veigas, G. Doria, P. Costa, J. Inácio, R. Martins, E. Fortunato, and P. V Baptista, "Portable optoelectronic biosensing platform for identification of mycobacteria from the Mycobacterium tuberculosis complex," *Biosens. Bioelectron.*, vol. 26, no. 5, pp. 2012–2017, Jan. 2011.

[43] B. Veigas, J. M. Jacob, M. N. Costa, D. S. Santos, M. Viveiros, J. Inácio, R. Martins, P. Barquinha, E. Fortunato, and P. V. Baptista, "Gold on paper-paper platform for Au-nanoprobe TB detection," *Lab Chip*, vol. 12, no. 22, pp. 4802–4808, Nov. 2012.

[44] S. Wang, S. Tasoglu, P. Z. Chen, M. Chen, R. Akbas, S. Wach, C. I. Ozdemir, U. A. Gurkan, F. F. Giguel, D. R. Kuritzkes, and U. Demirci, "Micro-a-fluidics ELISA for rapid CD4 cell count at the point-of-care," *Sci. Rep.*, vol. 4, p. 3796, Jan. 2014.

[45] Z. Gorocs and A. Ozcan, "On-chip biomedical imaging," *IEEE Rev. Biomed. Eng.*, pp. 29–46, 2013.

[46] S. Moon, H. O. Keles, A. Ozcan, A. Khademhosseini, E. Haeggstrom, D. Kuritzkes, and U. Demirci, "Integrating microfluidics and lensless imaging for point-of-care testing," *Biosens. Bioelectron.*, vol. 24, no. 11, pp. 3208–3214, Jul. 2009.

[47] F. Inci, O. Tokel, S. Wang, U. A. Gurkan, S. Tasoglu, D. R. Kuritzkes, and U. Demirci, "Nanoplasmonic quantitative detection of intact viruses from unprocessed whole blood," *ACS Nano*, May 2013.

[48] H. Shafiee, E. Lidstone, M. Jahangir, F. Inci, E. Hanhauser, T. J. Henrich, D. R. Kuritzkes, B. T. Cunningham, and U. Demirci, "Nanostructured optical photonic crystal biosensor for HIV viral load measurement," *Sci. Rep.*, vol. 4, p. 4116, Jan. 2014.

[49] D. Holmes, D. Pettigrew, C. H. C. H. Reccius, J. D. Gwyer, C. van Berkel, J. Holloway, D. E. Davies, H. Morgan, C. Van Berkel, and D. Morganti, "Leukocyte analysis and differentiation using high speed microfluidic single cell impedance cytometry," *Lab Chip*, vol. 9, no. 20, pp. 2881–2889, Oct. 2009.

[50] E. Du, S. Ha, M. Diez-Silva, M. Dao, S. Suresh, and A. P. Chandrakasan, "Electric impedance microflow cytometry for characterization of cell disease states," *Lab Chip*, vol. 13, no. 19, pp. 3903–3909, Oct. 2013.

[51] S. Ha, M. Diez-Silva, E. Du, S. Kim, and J. Han, "Microfluidic electric impedance spectroscopy for malaria diagnosis," *Miniaturized Syst. Chem. Life Sci.*, pp. 1960–1962, 2012.

[52] Y. Liu, T. Kwa, and A. Revzin, "Simultaneous detection of cell-secreted TNF-α and IFN-γ using micropatterned aptamer-modified

electrodes," *Biomaterials*, vol. 33, no. 30, pp. 7347–7355, Oct. 2012.

[53] Y. Liu, N. Tuleouva, E. Ramanculov, and A. Revzin, "Aptamer-based electrochemical biosensor for interferon gamma detection," *Anal. Chem.*, vol. 82, no. 19, pp. 8131–8136, Oct. 2010.

[54] M. De Souza Castilho and T. Laube, "Magneto immunoassays for Plasmodium falciparum histidine-rich protein 2 related to malaria based on magnetic nanoparticles," *Anal. Chem.*, pp. 5570–5577, 2011.

[55] M. K. Sharma, V. K. Rao, S. Merwyn, G. S. Agarwal, S. Upadhyay, and R. Vijayaraghavan, "A novel piezoelectric immunosensor for the detection of malarial Plasmodium falciparum histidine rich protein-2 antigen," *Talanta*, vol. 85, no. 4, pp. 1812–1817, Sep. 2011.

[56] Q. Guo, S. J. Reiling, P. Rohrbach, and H. Ma, "Microfluidic biomechanical assay for red blood cells parasitized by Plasmodium falciparum," *Lab Chip*, Feb. 2012.

[57] D. Gao, H. Liu, Y. Jiang, and J.-M. Lin, "Recent advances in microfluidics combined with mass spectrometry: Technologies and applications," *Lab Chip*, vol. 13, no. 17, pp. 3309–3322, Sep. 2013.

[58] World Health Organization, "Global health observatory data repository," 2013. [Online]. Available: http://apps.who.int/gho/data/

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