

DIAGNOSTICS

A smartphone dongle for diagnosis of infectious diseases at the point of care

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This work demonstrates that a full laboratory-quality immunoassay can be run on a smartphone accessory. This low-cost dongle replicates all mechanical, optical, and electronic functions of a laboratory-based enzyme-linked immunosorbent assay (ELISA) without requiring any stored energy; all necessary power is drawn from a smartphone. Rwandan health care workers used the dongle to test whole blood obtained via fingerprick from 96 patients enrolling into care at prevention of mother-to-child transmission clinics or voluntary counseling and testing centers. The dongle performed a triplexed immunoassay not currently available in a single test format: HIV antibody, treponemal-specific antibody for syphilis, and nontreponemal antibody for active syphilis infection. In a blinded experiment, health care workers obtained diagnostic results in 15 min from our triplex test that rivaled the gold standard of laboratory-based HIV ELISA and rapid plasma reagin (a screening test for syphilis), with sensitivity of 92 to 100% and specificity of 79 to 100%, consistent with needs of current clinical algorithms. Patient preference for the dongle was 97% compared to laboratory-based tests, with most pointing to the convenience of obtaining quick results with a single fingerprick. This work suggests that coupling microfluidics with recent advances in consumer electronics can make certain laboratory-based diagnostics accessible to almost any population with access to smartphones.

INTRODUCTION

Smartphones are being adopted at a breathtaking pace, including in developing countries (1, 2). They offer fast computing, a friendly user interface, and connectivity to data stored in the cloud (that is, servers accessible wirelessly), all at falling prices. Although smartphones are increasingly being adapted for health diagnostics, the most common applications have leveraged individual components and functions, such as cameras (3), data communication (4), and data processing (5), rather than replicating any complete diagnostic assay performed in clinical laboratories (6, 7).

We sought to build on previous work in miniaturizing diagnostics hardware (6, 8, 9) for the rapid point-of-care (POC) diagnosis of HIV, syphilis, and other sexually transmitted diseases. Early diagnosis and treatment of such diseases in pregnant mothers have been shown to reduce adverse health consequences to both mothers and their children (10). Treponemal antibodies appear earlier than nontreponemal antibodies in syphilis infection (11) and have been used in syphilis rapid diagnostic tests (RDTs). Recently, some manufacturers (Chembio, SD Bioline, and MedMira) have developed dual HIV/treponemal-syphilis tests, but these tests rely on lateral-flow or immunofiltration technologies, which could limit their performance and ability to multiplex

(12). We therefore sought to engineer all the capabilities of a benchtop enzyme-linked immunosorbent assay (ELISA) instrument into a small diagnostic accessory—a “dongle”—that attaches to a smartphone.

The dongle was designed to be small and light enough to fit in one hand and to run assays on disposable plastic cassettes with preloaded reagents, where disease-specific zones would provide an objective readout, similar to an ELISA microplate assay. The assay would be similar to an ELISA, but with gold nanoparticles and silver ions performing the amplification step instead of enzymes and substrate (13). For our assay targets, we chose HIV and treponemal syphilis antibody tests from our previous work (13) while detecting a third target, anti-cardiolipin antibody, as a nontreponemal syphilis marker. In addition, we added immunoglobulin M (IgM) as a secondary antibody for early syphilis detection (11). The U.S. Centers for Disease Control and Prevention (CDC) recommends a nontreponemal [for example, rapid plasma reagin (RPR)] test on all anti-treponemal enzyme immunoassay reactive specimens (14). However, a triplex test with HIV, treponemal syphilis, and nontreponemal syphilis results is not currently available commercially and clinically. As such, our device is advantageous in that it would help to characterize the infection as active or inactive [because treponemal syphilis antibody level remains high for life (11)], thus saving diagnostic time and simplifying treatment workflow (11, 14, 15).

Testing in the field can exhibit markedly different performance from tests run in a laboratory owing to variations in clinical specimens, local environmental conditions (including temperature and humidity), and variations in how the tests are run by individual users. In the field, sensitivities have been reported to be as low as 82% and specificities as low as 85% for the widely used HIV RDTs (16–18), 64 to 96% sensitivity and 97 to 99% specificity for treponemal syphilis antibody tests (Determine, SD Bioline, Syphicheck, VisiTest, and Chembio) (19–21), and 85% sensitivity and 96% specificity for nontreponemal

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syphilis antibody test (Chembio) (21) on whole blood (fingerprick or venipuncture) performed by trained staff. RDTs are also limited in number of markers in a single test, subjective user interpretation of band intensities, and lower sensitivity and reproducibility than laboratory-based tests.

Here, we demonstrate the field performance of three POC ELISA quality tests run simultaneously on a smartphone dongle under the following conditions: (i) the tests were run by health care workers (HCWs); (ii) the tests were run on fingerprick whole blood collected fresh from intended end users (patients); and (iii) the tests were run in a blinded manner where the reference laboratory results were unknown until testing of all subjects had concluded. In a 15-min assay, the dongle provided accurate diagnostic results on triplexed markers for HIV and syphilis, suggesting that laboratory-quality diagnostic services could be made accessible to any population with smartphones.

RESULTS

Dongle design for extremely low power consumption

The dongle (Fig. 1A) consists of two main innovations to achieve low power consumption. First, we eliminated the power-consuming electrical pump (6) by using a “one-push vacuum,” where a user mechanically activates a negative pressure chamber (Fig. 1B) to move a sequence of reagents prestored on a cassette (Fig. 1C). The simple vacuum chamber was created with a rubber bulb, with one port connected to the assay cassette outlet and one port to a silicone one-way valve. When the bulb is depressed, air exits out the one-way valve, and a spring aids the bulb in reexpansion, creating a negative pressure within the chamber that pulls liquids through the channels. The total flow times for a six-wash sequence were consistent between three users, with an average of 119 s (fig. S1). By contrast, our setup mechanically generates the vacuum source at the time of assay; this procedure is durable (similar to a bulb for a manual sphygmomanometer), requires little user training, and does not require maintenance and additional manufacturing to prepackage a vacuum source (which can also leak over time). Other components in the dongle, including robust and low-cost light-emitting diodes (LEDs), photodetectors (6, 13), and a microcontroller, consumed very low power. Using commercially available electronic components with an injection-moldable case, our device would have a manufacturing cost of \$34, in comparison to \$18,450 for typical ELISA equipment (Fig. 1D and table S1).

The dongle measured the optical density (OD) (absorbance) of silver enhancement on each assay (Fig. 2A), as described previously (13). Briefly, each detection zone was treated with capture proteins, and whole-blood sample flowed over each zone, followed by signal development reagents (gold-labeled antibodies, washes, and silver development solution), such that the concentration of analyte captured on each zone corresponded to the OD of silver enhancement. We designed the dongle so that power was only consumed during OD readings (8.5 mW, 8 s) and during information transfer back to the smartphone (1.5 mW, 8 min) (Fig. 2B). No power was consumed by the dongle while the sample and washes were flowing. Over a 15-min assay, the dongle had an average power consumption of 1.6 mW, or 0.22 mWh per test. By comparison, a typical smartphone uses 751 mW on a 3G network and 17.5 mW on standby mode (6), and a laser pointer uses about 1 to 5 mW (22). Using an Apple iPod touch (4th generation) to power the dongle, we found that each run con-

sumed about 2.4% of the battery, allowing 41 runs to be made on a single charge (note that newer generations of smartphones can hold more charge).

With such low power consumption by the dongle, we were able to implement a second innovation to remove the need for a battery: using the audio jack for transmitting power and for data transmission, as demonstrated by Kuo *et al.* (23). The audio jack connection (3.5 mm, 4 lead) has remained ubiquitous and standardized among smartphones, which allowed our dongle to be compatible with the growing variety of mobile phones and tablets. Here, a 19-kHz audio signal was sent from the iPod touch through the audio jack to the dongle and converted into a stable DC 3.0 V (fig. S2A). The dongle had no internal battery and used only the power delivered by the audio signal. The power harvested from the audio jack was stable and sufficient for reliable OD measurements compared with a benchtop analyzer (fig. S2B). For the target and positive control zones, there was no significant difference in OD measurements taken by the dongle and benchtop analyzer. The negative control zone showed a small but significant difference ($P = 0.03$, Student's *t* test). The dongle produced OD readings that correlated with a serial dilution of a strongly RPR-positive (1:128 titer) syphilis sample ($R^2 = 98.9\%$) (Fig. 2C).

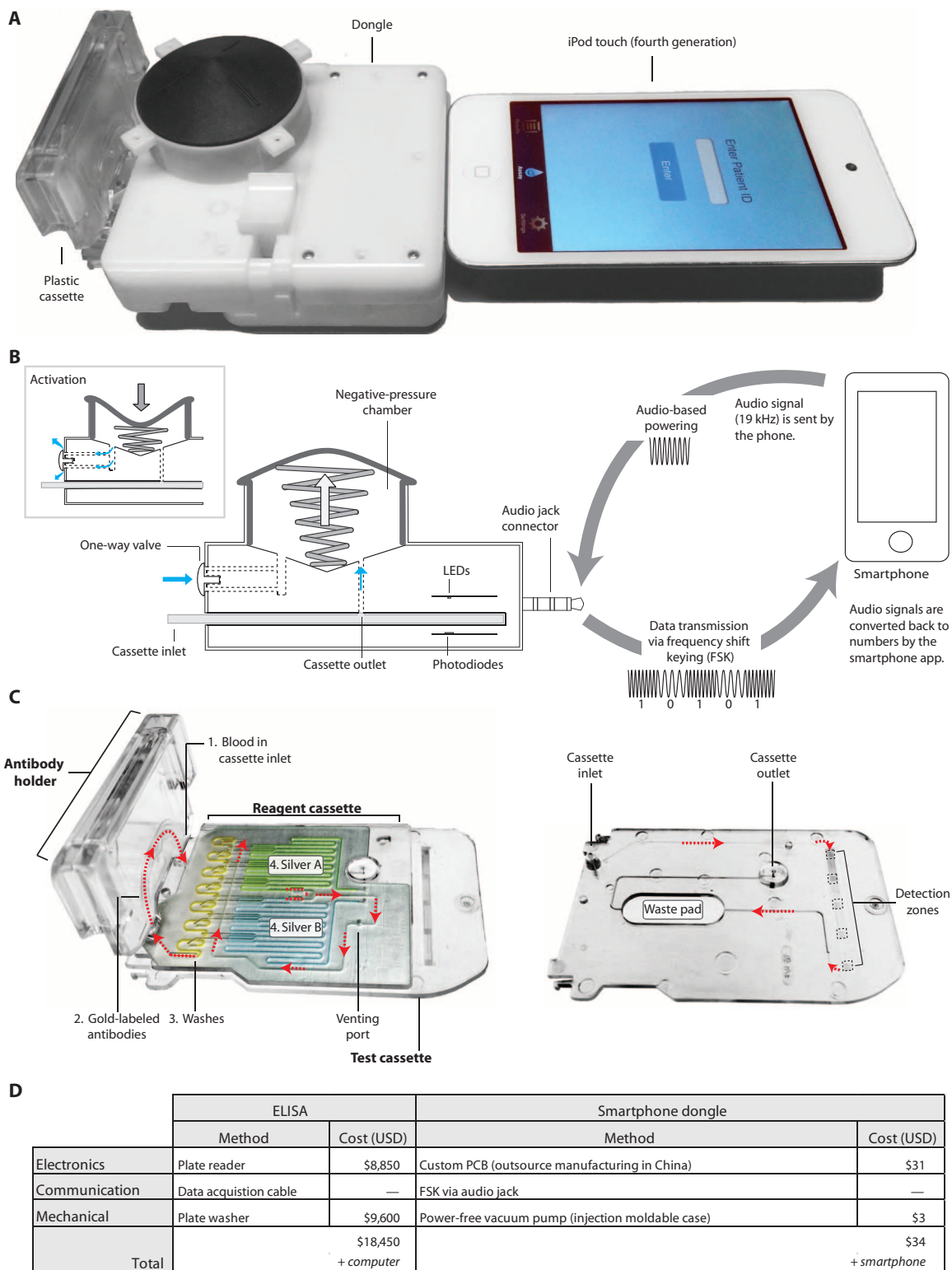
We programmed a microcontroller that performed FSK by converting a decimal integer into binary, and each bit was sent as a high-frequency (1632 Hz, or “1”) or low-frequency (816 Hz, or “0”) signal and transmitted the photodiode readings through the audio jack and back to the phone (Fig. 1B and fig. S2A). Our initial implementation was focused on fidelity of signal, but signal transmission can be sped up in the future. To test the accuracy of the signal, we programmed the microcontroller to send a pattern of alternating 1 and 0, or high- and low-frequency signals. We observed 100% accuracy for 12,160 bits tested. During the test, the custom smartphone application (“app”) on the phone converted the photodiode signals to absorbance units, which could be reported as “positive” or “negative” when above or below, respectively, a preset cutoff value.

Device function and operation

We built on our previous work for HIV/syphilis detection (13) in five major ways. First, we expanded the detection zones in the disposable microfluidic cassette from four to five zones, for detecting HIV, treponemal syphilis, and nontreponemal syphilis antibodies simultaneously with internal negative and positive controls (Fig. 1C). Second, gold-labeled IgM antibodies were added to the assay (Fig. 2D). Anti-cardiolipin antibodies are commonly found in IgM antibodies, and therefore, the addition of gold-labeled IgM offers enhanced sensitivity of nontreponemal syphilis. Third, to improve long-term stability in shipping and storage, we lyophilized gold-conjugated secondary antibodies inside the antibody holder, along with a stabilizer and anticoagulant, and packed the holder in an individual moisture barrier bag before shipping them to Rwanda. Lyophilized antibodies demonstrated comparable performance to gold-conjugated antibodies freshly diluted in buffer (Fig. 2E).

Fourth, to mimic field testing conditions, we prepared the test cassettes ahead of time at Columbia University before transporting them to Rwanda. By using the stabilizing agent StabilCoat during physisorption of capture proteins, the protein retained its function over 3 weeks at 60°C (fig. S3) [equivalent to roughly 28 weeks at 25°C according to Arrhenius-like approximations (24)]. This stabilizer was also found to be as effective as other blocking agents (fig. S4). Fifth, the wash buffers and silver reagents were preloaded on the reagent cassette each day before

Fig. 1. Overview of the dongle. (A) An image of the dongle with a microfluidic cassette connected to an iPod touch. (B) Schematic diagram of dongle highlighting a power-free vacuum generator using the audio jack connector for audio-based powering and frequency shift keying (FSK) data transmission to a smartphone or other smart-enabled device. Subfigure shows vacuum activation. (C) Left: A reagent cassette (top layer) that contains pre-stored reagents [washes (yellow) and silver A and B (blue and green)] and the test cassette (bottom layer) that contains five detection zones. Reagents are numbered in the order they flow through the test cassette. First, blood in the inlet flows through the channels, followed by gold-labeled antibodies resolubilized in 9 μ l of 1% bovine serum albumin (BSA)/0.05% Tween 20 in phosphate-buffered saline (PBS) and two 2- μ l 0.05% Tween 20 in PBS and four 2- μ l water washes with air gaps in between. Once the venting port is closed, silver A and B mix and flow through the channels. From the inlet, fluids move through each detection zone sequentially, then flowing into a waste pad where blood sample and reagents are collected without any fluids exiting the chip. The power-free vacuum chamber connects to the cassette outlet, drawing fluids from the inlet toward the waste pad. (D) Comparison of features of conventional ELISA (6) versus the dongle in terms of methods and cost for each main module required for the diagnostic test.



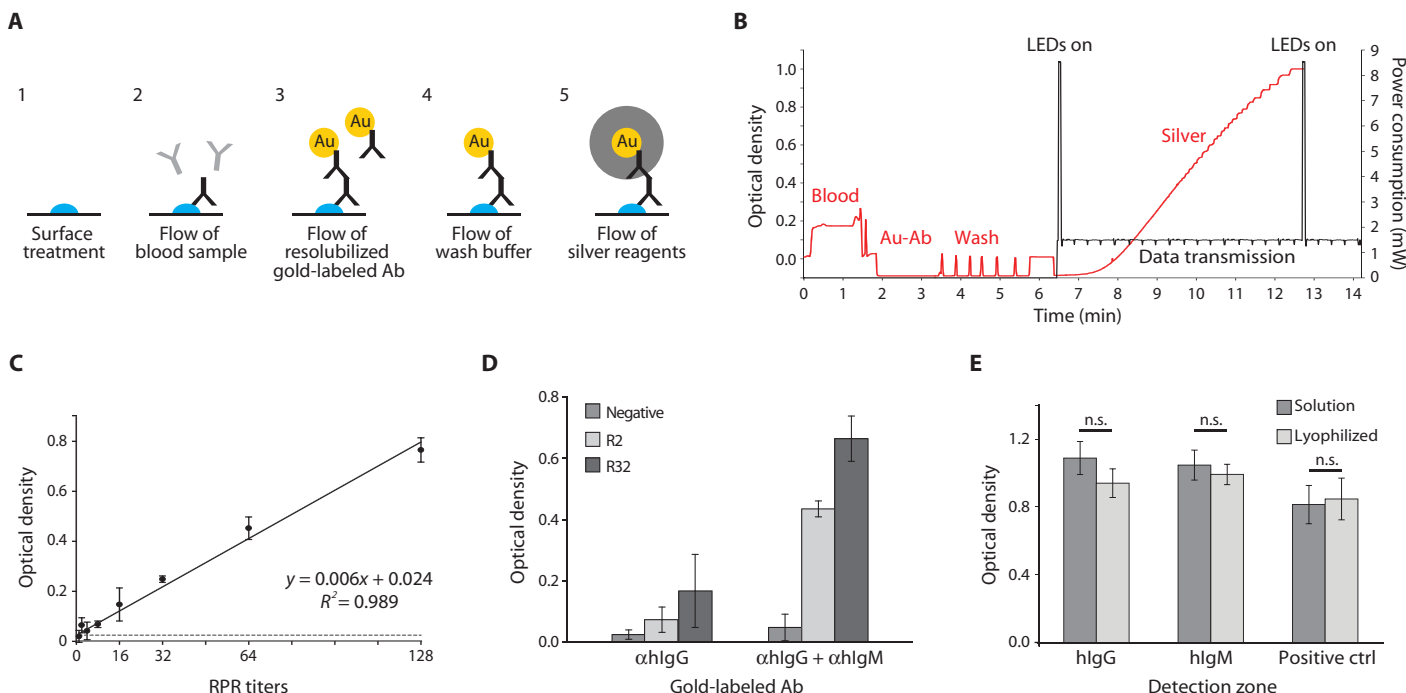


Fig. 2. Assay and field readiness. (A) Schematic diagram of assay reactions: (1) Each zone is individually treated with proteins, or none for negative control (ctrl). (2) Whole-blood sample is flowed through the channel, followed by (3) gold (Au)-labeled antibodies (Ab), (4) washes, and (5) silver reagents. (B) Power consumption of dongle (black) and OD of the HIV zone (red) during the assay. (C) Serial dilution of RPR-positive (1:128) serum to mimic lower RPR titers. Data are averages \pm SD ($n = 3$) and plotted with a linear regression fit and correlation. (D) Comparison of signal measurements obtained by addition of gold-labeled anti-human IgM (α hIgM) to gold-

labeled anti-human IgG (α hIgG) and gold-labeled anti-human IgG alone as detection antibodies for negative, weak positive nontreponemal syphilis [RPR titer, 1:2 (R2)], and strong positive nontreponemal syphilis [RPR titer, 1:32 (R32)] plasma samples. Data are averages \pm SD ($n = 4$ anti-human IgG; $n = 3$ anti-human IgG/anti-human IgM). (E) Comparison of signal from gold-labeled anti-human IgG and anti-human IgM antibodies lyophilized in a plastic antibody holder and freshly prepared in solution. Detection zones were functionalized with human IgG, human IgM, and rabbit anti-goat antibodies (positive ctrl). Data are averages \pm SD ($n = 3$). n.s., not significant; Student's t test.

testing. These conditions replicated real shipping and transportation conditions, minimized user steps, and increased field readiness to enable a “plug-and-play” operation for the user.

To perform the test, the user mixed 1 μ l of whole-blood sample with 9 μ l of diluent, placed \sim 2 μ l of the mixed sample into the cassette, attached the antibody holder into the cassette, inserted the cassette into the dongle, pressed the bulb fully to initiate vacuum, and pressed “start assay” on the app to start phase 1 of the test (Figs. 1 and 3A and fig. S5, A to D). After 5 min, all reagents downstream of the venting port (gold-labeled antibodies and washes) will have passed through the chip. For silver development, or phase 2, the user was then prompted to slide the toggle to close a venting port, to initiate flow and mixing of silver A and B (Fig. 1C). The two silver reagents were stable (and stored) separately; the venting port design allowed mixing of the silver reagents immediately before use, minimizing silver autocatalysis. To prevent exposure of chemicals to the user, sample and reagents were contained in a membrane filter within the cassette, and the antibody holder was securely connected to the cassette. OD readings were taken before and after silver development, and at the end of the assay (15 min), results for all markers are available and displayed on the app interface (fig. S5, E and F).

Field testing with target end users

The dongle app presented a user-friendly interface to aid the user through each test, step-by-step pictorial directions, built-in timers to

alert the user to next steps, and records of test results for later review (Fig. 3A and fig. S5). Given the simplicity of running the test, training of HCWs (laboratory technicians with no experience in ELISAs) took about 30 min. Five HCWs tested fresh fingerprick whole blood from 96 patients, whose disease statuses were unknown until the reference laboratory results were unblinded at the end of the study.

At three health centers in Kigali, Rwanda, HCWs recruited patient volunteers enrolled in preventing mother-to-child transmission (PMTCT) and voluntary counseling and testing (VCT) programs for the study, with our research team providing further information about the study to participants as needed. Consent forms were translated to Kinyarwanda (the principal local language) and obtained by a third-party translator fluent in English and Kinyarwanda. Fingerprick whole-blood specimens were collected and coded with a study ID number with no link to access other health information, to protect patient privacy. In parallel, venipuncture was performed on the same patients. For reference tests, HIV RDTs were completed at each site, whereas HIV ELISA, syphilis *Treponema pallidum* hemagglutination (TPHA), and syphilis RPR reference tests were performed at the Rwanda National Reference Laboratory using plasma.

The test results for detection of each marker were compared with the gold standard readout from laboratory-based HIV ELISA, TPHA, and RPR and are presented in terms of signal to cutoff of each target relative to its reference test (Fig. 3B and table S2). Cutoff values to determine if a sample was positive or negative for each marker were

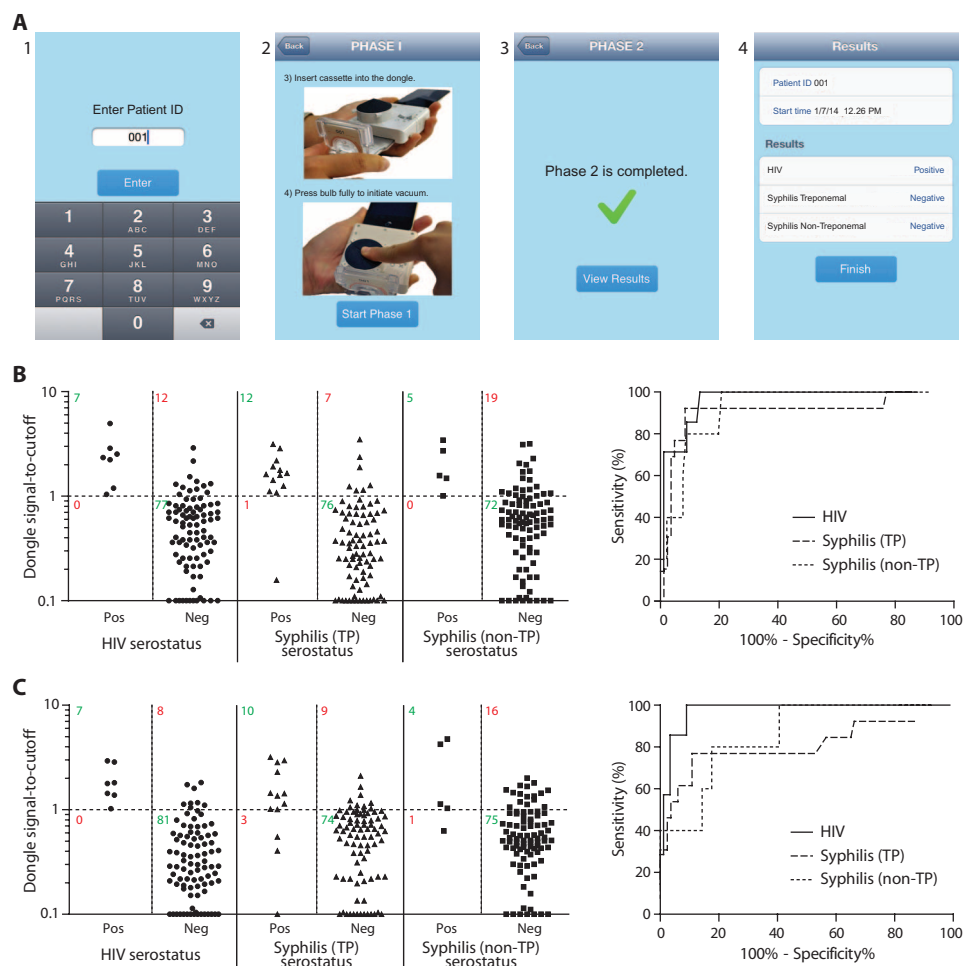


Fig. 3. Field trial in Rwanda. (A) User interface on a smartphone shows steps of dongle operation: (1) enter “Patient ID”; (2) step-by-step pictorial instructions starting from sample collection; (3) assay waiting time and status; and (4) results for each disease marker in format of “Positive,” “Negative,” or “Indeterminate.” (B) Third-party field testing of the dongle using clinical fingerprick whole-blood specimens. A vertical scatterplot shows dongle device signal-to-cutoff ratios of samples positive (Pos) or negative (Neg) for HIV, treponemal (TP) syphilis, and nontreponemal (non-TP) syphilis as determined by gold standard tests (HIV ELISA, TPHA, and RPR). An ROC curve is provided for each disease marker. (C) Field testing by the development team of the dongle using venipuncture whole-blood specimens. Vertical scatterplots and ROC curves for each disease marker.

selected by using receiver-operating characteristic (ROC) curves. Although a final product will offer preset cutoff values, in this development work, we identified cutoff values retrospective to data collection that maximize sensitivity (minimize false negatives) because our test is targeted toward screening applications. Cutoff values for internal negative and positive controls were also applied to verify validity of test results; no tests were excluded on the basis of these criteria. An indeterminate range (for example, if OD is within 10 to 20% of cutoff) (25) can be implemented for future tests to indicate the need to rerun the test.

The detection of HIV antibodies had a sensitivity of 100% [95% confidence interval (CI), 59 to 100%] and specificity of 87% (95% CI, 78 to 93%). Sensitivity for detection of treponemal antibodies was 92% (95% CI, 64 to 100%) with specificity of 92% (95% CI, 83 to 97%). Sensitivity for detection of anti-cardiolipin antibodies was 100% (95% CI, 48 to

100%) with specificity of 79% (95% CI, 69 to 87%). ROC curve shows area under the curve of 0.96 for HIV, 0.90 for treponemal syphilis, and 0.92 for nontreponemal syphilis (Fig. 3B). Specifically, table S2 shows results from the dongle that differed from reference tests, with one false-negative result for the treponemal syphilis test, and 12, 7, and 19 false-positive results for HIV, treponemal syphilis, and nontreponemal syphilis, respectively.

On venipuncture whole blood, the dongle yielded a sensitivity and specificity of 100% (95% CI, 59.0 to 100) and 91% (95% CI, 83.0 to 96.0) for HIV, 77% (95% CI, 46.2 to 95.0) and 89% (95% CI, 80.4 to 95.0) for treponemal syphilis, and 80% (95% CI, 28.4 to 99.5) and 82% (95% CI, 73.0 to 89.6) for nontreponemal syphilis (Fig. 3C). There was no significant difference of dongle assay performance on fingerprick and venous whole blood for HIV ($P = 0.45$), treponemal syphilis ($P = 1.0$), and nontreponemal syphilis ($P = 0.33$), using McNemar test.

Subsequent to the field trial, we found that cassettes with an increased concentration of coated proteins could take neat (undiluted) whole blood and produce accurate results (fig. S6 and table S3). The HIV antigen (10 $\mu\text{g/ml}$) spotting concentration yielded 100% sensitivity (95% CI, 78.20 to 100) and specificity (95% CI, 29.24 to 100), compared to those spotted with antigen (2 $\mu\text{g/ml}$), which yielded 86.67% sensitivity (95% CI, 59.94 to 98.34) and 33.33% specificity (95% CI, 0.84 to 90.57).

Patient survey

To assess user feedback, a third-party interviewer fluent in English and Kinyarwanda conducted the surveys to reduce any biases from the study team. The questions posed to the participants focused on dongle/fingerprick preference versus traditional

venipuncture (and why), desired test time, and whether the dongle would be recommended (and why) (Fig. 4). A vast majority of patients (97%) would recommend the dongle to others because of the fast turnaround time (57%), potential to offer results for multiple diseases (44%), and simplicity of procedure (29%). Fingerprick blood collection was preferred to conventional venipuncture by 95% of patients because it is less painful (98%), it takes shorter time (60%), the HCW had trouble with the needle collection (55%), the patient is scared of a needle (43%), and a fingerprick takes less volume of blood (42%). However, 2% of patients preferred venipuncture because they trust the result more with venous blood (Fig. 4). HCWs appreciated the lack of user interpretation to read the result or external power to operate and also noted in surveys that the dongle could be useful in low-volume testing sites (for example, VCT or mobile visit) or serve as a backup test for high-volume

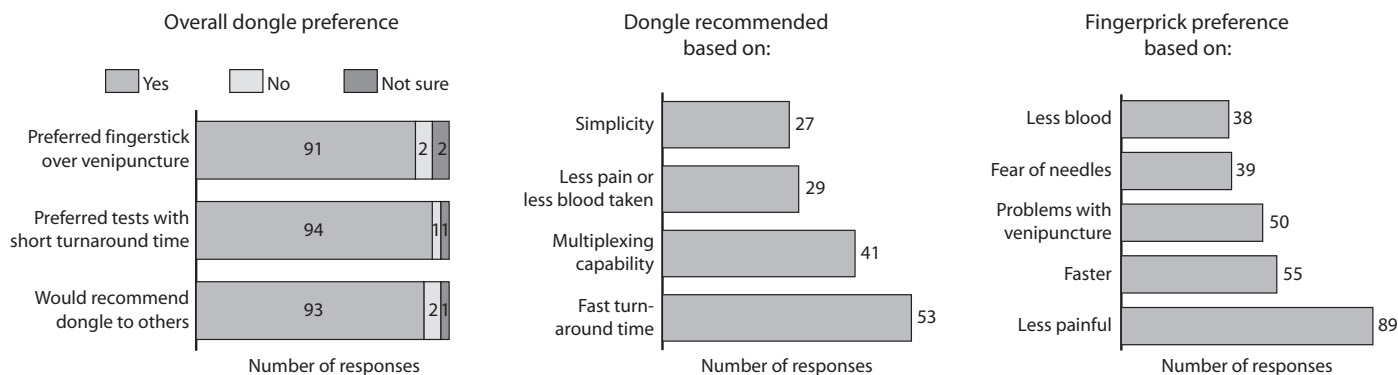


Fig. 4. Satisfaction survey from participants in this study.

patients' clinics in case of power outage, which we experienced during testing.

DISCUSSION

This dongle presents new capabilities for users ranging from health care providers to consumers. For HCWs, management of infectious diseases could be improved with access to multiplexed test at the POC. For example, for syphilis, health impact modeling has suggested that a test with only 70 to 80% sensitivity and specificity, but performed at the POC, can reduce deaths by 10-fold over a hypothetically perfectly accurate laboratory-based test (26) by increasing detection of infections. For large-scale screening, high sensitivity (with few false negatives) is most important, as is achieved by the dongle. For HIV, scaling up HIV testing at the community level with immediate antiretroviral therapy could nearly stop HIV transmission and approach elimination of the virus (27).

The dual test for syphilis holds clinical value for HCWs. The current procedure in many developing countries calls for a single laboratory-based qualitative RPR test for syphilis, such that all patients with positive nontreponemal results are recommended for treatment. Because this procedure can lead to overtreatment, given the intrinsic lower specificity of nontreponemal assays (14, 15), several countries are adopting treponemal-specific RDTs (28). However, blanket treatment of patients testing positive with a treponemal-specific RDT can lead to overtreatment and penicillin resistance, because treponemal antibodies remain even after infection has cleared. A dual nontreponemal and treponemal syphilis test would empower HCWs to follow guidelines (14, 15) that recommend treatment under two scenarios: if both tests are positive, or if treponemal-specific results are positive and the patient either had no previous infection or exhibits signs of new infection. Differentiation between active and past infection is particularly valuable in endemic areas, including Rwanda (29). In addition, compared to syndromic management (11), POC syphilis tests also help HCWs avoid overtreatment and improve cost-effectiveness; among our subject group, 13 patients exhibited positive TPHA results—although only 4 exhibited positive RPR results—and would all be treated under guidelines with rapid treponemal-specific tests.

It is challenging to use RDTs to detect multiple markers. The dongle is versatile in that it can detect selectively IgM and/or IgG antibodies on multiple markers. This capability supports early detection of syph-

ilis, because anti-treponemal IgM antibodies appear earlier than anti-treponemal IgG by 2 weeks (11). Addition of a nontreponemal test and detection of IgM—performed alongside HIV—moves another step toward a complete POC multiplex antenatal-care panel. Performing three individual commercially available tests can cost up to \$8.50 [\$0.80 to \$5 for HIV RDT (30), \$1 to \$3 for treponemal RDT (15), and \$0.50 for RPR (31)]. By comparison, material and reagent cost per test for our triplex test is \$1.44, leaving room for a substantially lower anticipated market price. In addition, compared to RDTs, the dongle offers automation of assay, objective readout of signal, and quantitation, although it requires more instrumentation than RDTs. RDTs present challenges for untrained users to execute precise liquid handling and metering, particularly in multistep tests. Our system contains precise injection-molded cassettes, preloaded reagents, optimized optics, and exact alignment that can reduce user variability. Add-on optical readers are becoming available for RDTs but still present challenges to the user (for example, in positioning and illumination accuracy) because RDTs are originally designed to be single-step stand-alone tests (32).

Two practical challenges to deploying POC diagnostic devices are specimen collection and infrastructure of facilities. This dongle test required one fingerprick or 2 μ l of whole blood for all three tests (avoiding multiple fingerpricks, a point appreciated by the patients in the survey), where HIV and syphilis RDTs require anywhere from 5 to 60 μ l each. Another challenge to blood analysis in resource-poor settings is power outages, which is obviated with our audio jack-powered dongle. We show that when so little power is needed for diagnostics, the audio jack connection can power and record an entire laboratory-level immunoassay with amplification and washing reagents (Fig. 2B). Although the audio jack connection has been used for data communication in devices, including for heart rate monitoring (33), measuring exhaled carbon monoxide in smokers (34), and electrochemical sensing (8), it has been less adapted for powering health diagnostics devices, typically owing to large energy consumption.

Consumer adoption of health-monitoring devices is increasing rapidly. This dongle takes a step toward coupling microfluidics with advances in consumer electronics. The hardware of the dongle exhibits characteristics similar to familiar consumer electronics devices through a number of technical innovations: low power (using a power-free, continuous-flow vacuum and requiring no power), durable components (using LEDs and photodetectors), and portability. Our system generates a reliable, repeatable vacuum at the time of the assay while keeping the consumables simple to manufacture, building on previous methods to

simplify the fluid movement steps, such as vacuum (13) and degas-driven flow (35). We also considered the manufacturability, shipping, and storage of the tests by manufacturing the cassettes and precoating them with proteins and stabilizing agents before shipping to the use location.

In addition, we lyophilized gold-labeled antibodies and anticoagulant onto the antibody holder to increase storage time. The most important feature behind a plug-and-play experience is the reduction of manual steps, enabled by integrating advances in fluidics and mechanical, optical, and electronic components. In the future, robot-assisted loading of reagent cassettes could be implemented, because the reagents were stable for over 6 months at room temperature (13, 36) and wash plugs have been shown to stay separated after airborne shipping (37). To enhance the user experience, we built a touch-activated pictorial software interface that allowed for training in 30 min, a step-by-step software guide on the smartphone contemporaneous with assay operation, and reporting of results (yes/no or quantitative titers) without user interpretation. As a result, patients expressed satisfaction with the dongle, citing the 15-min turnaround time as the biggest benefit, because a third of patients wait more than 2.5 hours to receive their results (personal communication with patients). Overall, the combined hardware, software, and microfluidic specifications suggest that new consumer-oriented medical devices are on the precipice of moving beyond glucose monitoring, vital signs, and wellness into clinical diagnostics for endemic diseases, including HIV and syphilis.

MATERIALS AND METHODS

Study design

The goal of this study was to develop a power-free lab-on-a-chip device for HIV and syphilis diagnosis in resource-limited settings. To evaluate dongle performance, the device was deployed in Rwanda, into the hands of HCWs who did not have ELISA training, for prospective diagnosis of patients already scheduled to receive HIV and syphilis testing. This study was approved by Columbia University Institutional Review Board (IRB) and Rwanda National Ethics Committee. Study sites were selected from the highest HIV/syphilis prevalence in the PMTCT group, based on 2013 routine data from the HIV division at Rwanda Biomedical Center. We selected three community-level health centers (Kimironko, Biryogo, and Gahanga) in Kigali with guidance from HIV/AIDS and STIs Diseases Division, Rwanda Biomedical Center, based on incidence of disease and willingness to participate in the study. HCWs involved in the study were laboratory technicians at the health centers and selected on the basis of willingness to participate in the study (Supplementary Materials and Methods). All patients who were enrolled in PMTCT or VCT programs over a 2-week period and who provided consent participated in this study. We did not perform power analysis; instead, we chose a sample size of ~100, which allowed us to focus on incorporating device testing with clinic flow, getting user feedback, and assessing patient reception, in resource-limited settings. Additional patient information is in Supplementary Materials and Methods.

After sample collection, patients were given a short survey about their experiences by a third-party translator. Patients were compensated 1000 RWF (Rwandan Franc) (\$1.54) for their participation. Disease statuses were blinded to the Columbia team and HCWs who conducted the test. HIV RDTs (Colloidal Gold, Determine, and Uni-Gold) were completed at each site. HIV ELISA (Vironostika), syphilis TPHA

(Spinreact), and RPR (Spinreact) as reference tests were performed at Rwanda National Reference Laboratory using plasma separated from venipuncture blood. At the end of the trial, the results were unblinded to the study team, and reference test results were compared to the results obtained by the dongle.

Dongle design and manufacture

Custom-printed circuit boards were designed in Altium and printed from PCB Universe. A bill of materials and the circuit diagram are provided (table S1 and fig. S7). LEDs and photodiodes were precisely aligned with the cassette slot so that testing zones aligned without manual effort. One-millimeter pinholes made of 1-mm-thick black Delrin (McMaster-Carr) were aligned above each photodiode to prevent stray light. The dongle casing was designed in SolidWorks and printed in-house (Objet24 3D Printer, Stratasys). Vacuum chamber was created with a one-way umbrella valve (Minivalve), a rubber bulb from a 140-ml syringe (Becton Dickinson), and a conical spring (Century Spring Corp.) inside to aid reexpansion. Silicone rubber O-rings and sheets (McMaster-Carr) were used to connect to outlet and seal the venting port. Power-free fluid flow, signal readout, and audio jack powering and signal transmission are provided in Supplementary Materials and Methods.

Cassette preparation

All cassettes were prepared at Columbia University before transporting to Rwanda. We added disease-specific proteins to the cassette surface by direct physisorption with a stabilizing agent (StabilCoat, SurModics), except cardiolipin, which was covalently attached to the plastic surface using EDC-sulfo-NHS reaction (Supplementary Materials and Methods). We used robot-assisted manufacturing (adapted from OPKO Diagnostics) for reproducible and high-throughput cassette preparation. We selected recombinant multiepitope chimeric antigens (gp41, gp36, and O-IDR) for an HIV 1/2 (BioLink International) marker, a 17-kD recombinant outer membrane protein TpN17 (Lee Laboratories) (6, 13) for a treponemal syphilis marker, synthetic cardiolipin prepared from plant source (38) provided by CDC for a nontreponemal syphilis marker, and rabbit anti-goat IgG (Life Technologies) for a positive control. For an internal negative control (provide background signal), the surface was not functionalized with any protein but treated with blocking agent. Gold-labeled anti-human IgG and IgM antibodies were lyophilized inside the antibody holder by OPKO Diagnostics.

Each day before testing at the clinic site, two 2- μ l PBS–0.05% Tween 20 and four 2- μ l water washes as well as 60 μ l each of silver nitrate (silver A) and silver reducing agent (silver B) were loaded to the reagent cassette manually by pipetting and sealed using an adhesive tape (OPKO Diagnostics) to mimic prepackaged reagents (Fig. 2A).

Device operation

To perform the test, the user (HCW) collected fingerprick whole blood using conventional methods. One microliter of whole blood was then diluted with 9 μ l of 1% BSA–0.05% Tween 20 in PBS, and 2 μ l of the mixed sample was pipetted onto the disposable test cartridge (fig. S5B). Cassette preparation is described in Supplementary Materials and Methods. The user inserted the antibody holder (prefilled with 9 μ l of 3% BSA–0.05% Tween–PBS) into a microfluidic cassette, inserted the cassette into the dongle, and pressed the bulb fully to initiate vacuum (fig. S5, C and D). After 5 min, the user was prompted to move a toggle to close a venting port and to initiate silver development for 9 min.

Afterwards, results for all markers were displayed on the screen (fig. S5F), and raw absorbance values were recorded along with the study ID.

Each patient venipuncture whole blood was tested by the Columbia team in parallel with fingerprick blood testing. An aliquot of venipuncture whole blood (~50 μ l) was made from each whole blood collected. Venipuncture whole blood was processed in the same manner as the fingerprick blood.

Post-field test optimization in the laboratory is described in Supplementary Materials and Methods.

Pilot field trial

Study sites, HCWs, populations, and confidentiality agreements, as well as dongle operation training and testing are described in Supplementary Materials and Methods.

Statistics

Averages, SDs, linear fit, and two-sided Student's *t* tests ($\alpha = 0.05$) were calculated with Microsoft Excel. Student's *t* test was chosen to compare two small sets of quantitative data when data in each sample set were related. Vertical scatterplots, sensitivity, specificity, 95% CIs, ROC curves, and McNemar test were created in GraphPad Prism.

SUPPLEMENTARY MATERIALS

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Materials and Methods

Fig. S1. User-activated negative pressure-driven flow.

Fig. S2. Smartphone-dongle interface and comparison with benchtop analyzer.

Fig. S3. Stability of functionalized protein on microfluidic cassette.

Fig. S4. Comparison of blocking agents.

Fig. S5. Step-by-step illustration of dongle testing.

Fig. S6. Optimization of dongle HIV assay using undiluted whole-blood samples.

Fig. S7. Circuit diagram of dongle.

Table S1. Bill of dongle materials and cost per component.

Table S2. Raw data from field testing in three Rwandan clinics with reference results.

Table S3. Raw data from venipuncture whole blood from Columbia University Medical Center (CUMC) with reference results for optimization of HIV antigen concentration.

REFERENCES AND NOTES

- Ericsson, "Ericsson Mobility Report: On the pulse of the networked society" (2014).
- A. Fitzpatrick, Mozilla's \$25 smartphone is a brilliant gamechanger, *Time* (2014).
- Q. Wei, H. Qi, W. Luo, D. Tseng, S. J. Ki, Z. Wan, Z. Göröcs, L. A. Bentolila, T. T. Wu, R. Sun, A. Ozcan, Fluorescent imaging of single nanoparticles and viruses on a smart phone. *ACS Nano* **7**, 9147–9155 (2013).
- D. Zurovac, R. K. Sudoi, W. S. Akhwale, M. Ndiritu, D. H. Hamer, A. K. Rowe, R. W. Snow, The effect of mobile phone text-message reminders on Kenyan health workers' adherence to malaria treatment guidelines: A cluster randomised trial. *Lancet* **378**, 795–803 (2011).
- C. C. Freifeld, R. Chunara, S. R. Mekaru, E. H. Chan, T. Kass-Hout, A. Ayala Iacucci, J. S. Brownstein, Participatory epidemiology: Use of mobile phones for community-based health reporting. *PLOS Med.* **7**, e1000376 (2010).
- C. D. Chin, Y. K. Cheung, T. Laksanasopin, M. M. Modena, S. Y. Chin, A. A. Sridhara, D. Steinmiller, V. Linder, J. Mushingantahe, G. Umvilighozo, E. Karita, L. Mwambarangwe, S. L. Braunstein, J. van de Wijgert, R. Sahabo, J. E. Justman, W. El-Sadr, S. K. Sia, Mobile device for disease diagnosis and data tracking in resource-limited settings. *Clin. Chem.* **59**, 629–640 (2013).
- V. Onescu, M. Mancuso, D. Erickson, Cholesterol testing on a smartphone. *Lab Chip* **14**, 759–763 (2014).
- A. Nemiroski, D. C. Christodouleas, J. W. Hennek, A. A. Kumar, E. J. Maxwell, M. T. Fernández-Abedul, G. M. Whitesides, Universal mobile electrochemical detector designed for use in resource-limited applications. *Proc. Natl. Acad. Sci. U.S.A.* **111**, 11984–11989 (2014).
- D. S. Lee, B. G. Jeon, C. Ihm, J. K. Park, M. Y. Jung, A simple and smart telemedicine device for developing regions: A pocket-sized colorimetric reader. *Lab Chip* **11**, 120–126 (2011).
- M. Genç, W. J. Ledger, Syphilis in pregnancy. *Sex. Transm. Infect.* **76**, 73–79 (2000).
- R. W. Peeling, H. Ye, Diagnostic tools for preventing and managing maternal and congenital syphilis: An overview. *Bull. World Health Organ.* **82**, 439–446 (2004).
- P. Yager, G. J. Domingo, J. Gerdes, Point-of-care diagnostics for global health. *Annu. Rev. Biomed. Eng.* **10**, 107–144 (2008).
- C. D. Chin, T. Laksanasopin, Y. K. Cheung, D. Steinmiller, V. Linder, H. Parsa, J. Wang, H. Moore, R. Rouse, G. Umvilighozo, E. Karita, L. Mwambarangwe, S. L. Braunstein, J. van de Wijgert, R. Sahabo, J. E. Justman, W. El-Sadr, S. K. Sia, Microfluidics-based diagnostics of infectious diseases in the developing world. *Nat. Med.* **17**, 1015–1019 (2011).
- Centers for Disease Control and Prevention, Sexually transmitted diseases treatment guidelines. *MMWR Morb. Mortal Wkly. Rep.* **59**, 26–29 (2010).
- A. C. Seña, B. L. White, P. F. Sparling, Novel *Treponema pallidum* serologic tests: A paradigm shift in syphilis screening for the 21st century. *Clin. Infect. Dis.* **51**, 700–708 (2010).
- D. K. Plate, Rapid HIV Test Evaluation Working Group, Evaluation and implementation of rapid HIV tests: The experience in 11 African countries. *AIDS Res. Hum. Retroviruses* **23**, 1491–1498 (2007).
- K. P. Delaney, B. M. Branson, A. Uniyal, S. Phillips, D. Candal, S. M. Owen, P. R. Kerndt, Evaluation of the performance characteristics of 6 rapid HIV antibody tests. *Clin. Infect. Dis.* **52**, 257–263 (2011).
- S. C. Kagulire, P. Opendi, P. D. Stamper, J. L. Nakavuma, L. A. Mills, F. Makumbi, R. H. Gray, J. P. Shott, D. Serwadda, S. J. Reynolds, Field evaluation of five rapid diagnostic tests for screening of HIV-1 infections in rural Rakai, Uganda. *Int. J. STD AIDS* **22**, 308–309 (2011).
- J. Li, H. Y. Zheng, L. N. Wang, Y. X. Liu, X. F. Wang, X. R. Liu, Clinical evaluation of four recombinant *Treponema pallidum* antigen-based rapid diagnostic tests for syphilis. *J. Eur. Acad. Dermatol. Venerol.* **23**, 648–650 (2009).
- Y. Jafari, R. W. Peeling, S. Shivkumar, C. Claessens, L. Joseph, N. P. Pai, Are *Treponema pallidum* specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? Evidence from a meta-analysis. *PLOS One* **8**, e54695 (2013).
- Y. P. Yin, X. S. Chen, W. H. Wei, K. L. Gong, W. L. Cao, G. Yong, L. Feng, S. J. Huang, D. M. Wang, Y. Han, S. C. Chen, D. Mabey, R. W. Peeling, A dual point-of-care test shows good performance in simultaneously detecting nontreponemal and treponemal antibodies in patients with syphilis: A multisite evaluation study in China. *Clin. Infect. Dis.* **56**, 659–665 (2013).
- R. C. Habberset, M. A. Naivar, T. A. Woods, G. R. Goddard, S. W. Graves, Evaluation of a green laser pointer for flow cytometry. *Cytometry A* **71**, 809–817 (2007).
- Y.-S. Kuo, S. Verma, T. Schmid, P. Dutta, Hijacking power and bandwidth from the mobile phone's audio interface, in *First Annual Symposium on Computing for Development (DEV'10)*, (ACM, London, UK, 2010), p. 24.
- G. Anderson, M. Scott, Determination of product shelf life and activation energy for five drugs of abuse. *Clin. Chem.* **37**, 398–402 (1991).
- J. He, S. Parker, Qualitative immunoassays, in *The Immunoassay Handbook: Theory and Applications of Ligand Binding and Related Techniques*, D. Wild, Ed. (Elsevier Science, Oxford, UK, ed. 4, 2013).
- J. E. Aledort, A. Ronald, M. E. Rafael, F. Gironi, P. Vickerman, S. M. Le Blancq, A. Landay, K. Holmes, R. Ridzon, N. Hellmann, M. V. Shea, R. W. Peeling, Reducing the burden of sexually transmitted infections in resource-limited settings: The role of improved diagnostics. *Nature* **444** (Suppl. 1), 59–72 (2006).
- R. M. Granich, C. F. Gilks, C. Dye, K. M. De Cock, B. G. Williams, Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: A mathematical model. *Lancet* **373**, 48–57 (2009).
- D. C. Mabey, K. A. Sollis, H. A. Kelly, A. S. Benzaken, E. Bitarakwate, J. Changalucha, X. S. Chen, Y. P. Yin, P. J. Garcia, S. Strasser, N. Chintu, T. Pang, F. Terris-Prestholt, S. Sweeney, R. W. Peeling, Point-of-care tests to strengthen health systems and save newborn lives: The case of syphilis. *PLOS Med.* **9**, e1001233 (2012).
- Centers for Disease Control and Prevention, Notice to readers: Recommendations regarding screening of refugee children for treponemal infection. *MMWR Morb. Mortal Wkly. Rep.* **54**, 933–934 (2005).
- A. Johnson, *HIV Test Kits Listed in the USAID Source and Origin Waiver: Procurement Information Document* (Management Sciences for Health, Arlington, VA, ed. 5, 2009).
- M. J. Binnicker, J. D. Yao, F. R. Cockerill III, Non-treponemal serologic tests: A supplemental, not confirmatory testing approach. *Clin. Infect. Dis.* **52**, 274–275; author reply 275–276 (2011).
- K. Faulstich, R. Gruler, M. Eberhard, D. Lentzsch, K. Haberstroh, Handheld and portable reader devices for lateral flow immunoassays, in *Lateral Flow Immunoassay* (2009), (Humana Press, New York, NY pp. 157–183).
- S. Nirjon, R. F. Dickerson, Q. Li, P. Asare, J. A. Stankovic, D. Hong, B. Zhang, X. Jiang, G. Shen, F. Zhao, Musicalheart: A hearty way of listening to music, in *Proceedings of the 10th ACM Conference on Embedded Network Sensor Systems*, Toronto, Ontario, Canada, 2012, pp: 43–56 DOI: 10.1145/2426656.2426662.
- S. E. Meredith, A. Robinson, P. Erb, C. A. Spieler, N. Klugman, P. Dutta, J. Dallery, A mobile-phone-based breath carbon monoxide meter to detect cigarette smoking. *Nicotine Tob. Res.* **16**, 766–773 (2014).

35. I. K. Dimov, L. Basabe-Desmonts, J. L. Garcia-Cordero, B. M. Ross, Y. Park, A. J. Ricco, L. P. Lee, Stand-alone self-powered integrated microfluidic blood analysis system (SIMBAS). *Lab Chip* **11**, 845–850 (2011).
36. W. Wang, Lyophilization and development of solid protein pharmaceuticals. *Int. J. Pharm.* **203**, 1–60 (2000).
37. V. Linder, S. K. Sia, G. M. Whitesides, Reagent-loaded cartridges for valveless and automated fluid delivery in microfluidic devices. *Anal. Chem.* **77**, 64–71 (2005).
38. A. R. Castro, W. E. Morrill, W. A. Shaw, D. C. Gale, M. M. Park, L. A. Peregrino-Ferreira, M. L. Bazzo, V. Pope, Use of synthetic cardiolipin and lecithin in the antigen used by the Venereal Disease Research Laboratory test for serodiagnosis of syphilis. *Clin. Diagn. Lab. Immunol.* **7**, 658–661 (2000).

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A smartphone dongle for diagnosis of infectious diseases at the point of care

Tassaneewan Laksanasopin, Tiffany W. Guo, Samiksha Nayak, Archana A. Sridhara, Shi Xie, Owolabi O. Olowookere, Paolo Cadinu, Fanxing Meng, Natalie H. Chee, Jiyoung Kim, Curtis D. Chin, Elisaphane Munyazesa, Placidie Mugwaneza, Alex J. Rai, Veronicah Mugisha, Arnold R. Castro, David Steinmiller, Vincent Linder, Jessica E. Justman, Sabin Nsanzimana and Samuel K. Sia

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Dongle + app = mobile test for sexually transmitted diseases

There are thousands of health-related "apps" for smartphones, from tracking sleep patterns to recording heart rate to logging caloric intake. The power of such apps in connecting resource-limited communities to health care workers and, in turn, to proper and immediate care is now emerging. In this issue, Laksanasopin and colleagues describe a microfluidic-based diagnostic test for HIV and syphilis that attaches to (and is powered by) the iPod's headphone jack. The mobile test also comes complete with an easy-to-use app, flashing test results on-screen in under 15 min. The test is based on the standard immunoassay but uses gold-labeled antibodies to detect HIV and syphilis antigens in only 2 μ l of whole blood, and then silver reagents to amplify the resulting signal. The authors deployed the dongle in Rwanda, testing its sensitivity and specificity on 96 patients. Evaluated side by side with the gold standard tests for HIV and syphilis, the dongle produced results with a sensitivity and specificity needed for making treatment decisions in the field. In a survey, a vast majority of patients reported satisfaction with dongle performance. After a few next-generation tweaks, including reducing the size of the dongle, the entire diagnostic package is ready for adoption in resource-poor clinics and communities, to improve detection of HIV and syphilis and empower health care workers to administer timely and appropriate treatments.

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