Next-generation lab-on-a-chip devices

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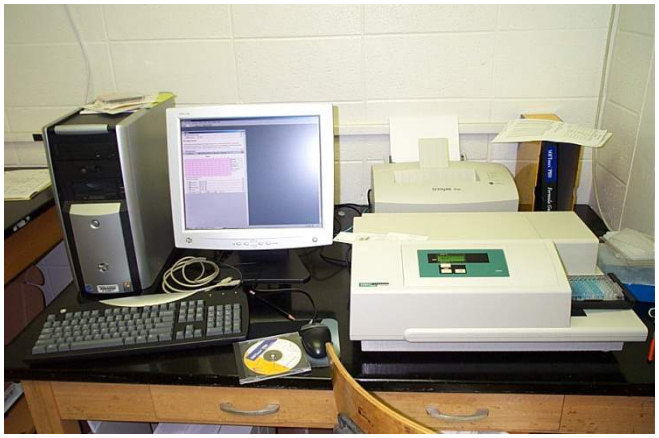
Columbia University

APHL, Little Rock
June 4, 2014

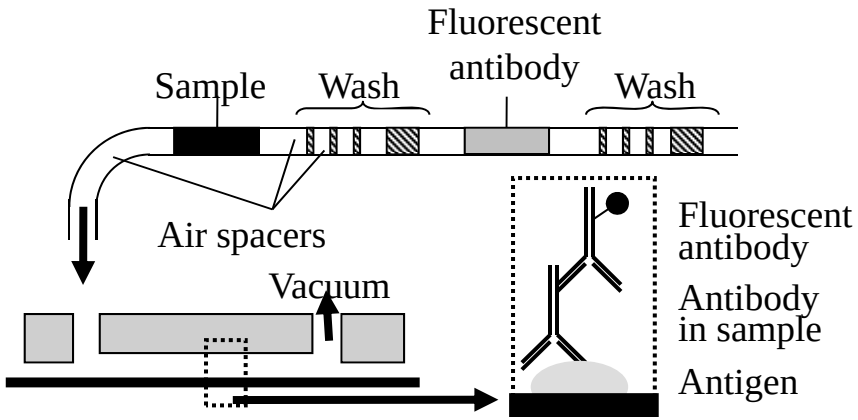
Clinical ELISA testing...

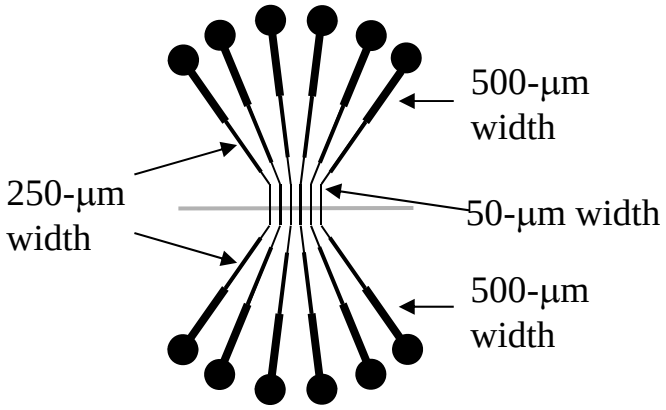


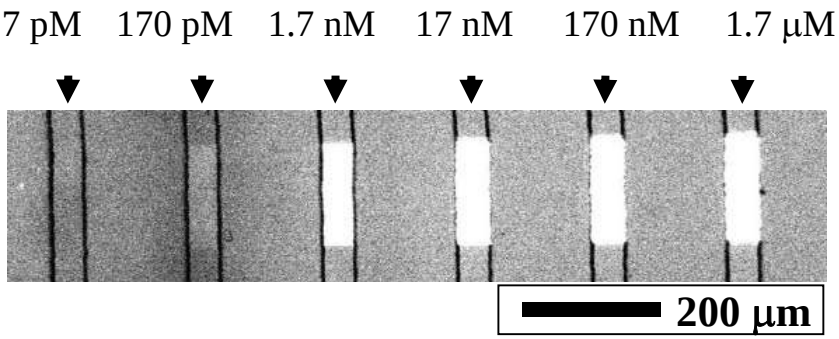
- coat surface with antigen (overnight)
- block with 1% BSA or 0.05% Tween-20 (1 hr)
- add sample containing antibody to be tested (1 hr)
- add enzyme-conjugated antibody (1 hr)
- add substrate (10 min.)

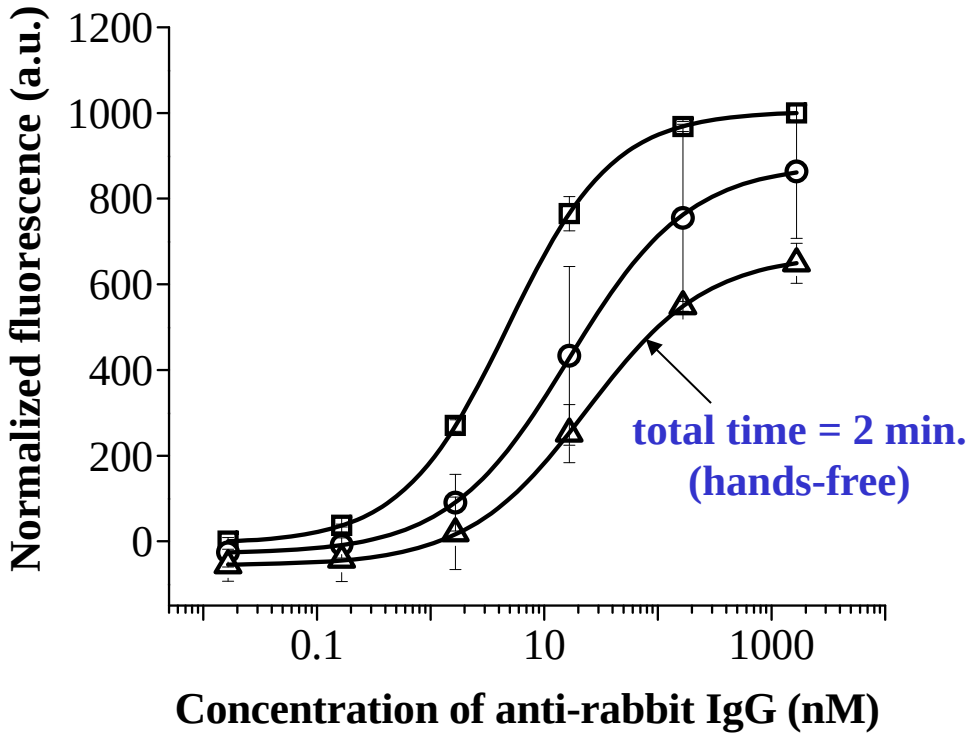
	ELISA	ideal method
low cost? - capital - per test	 ✓	✓ ✓
compact?		✓
rapid?		✓
simple to operate?		✓
sensitive (pM)?	✓	✓
distinguishes quantitative differences?	✓	✓
amenable to parallel analysis?	✓	✓
operable without ground electricity?		✓
works in field conditions (sunlight)?		✓
uses accessible reagents?	✓	✓

“Plug-in cartridge” (bubble-based reagent delivery)



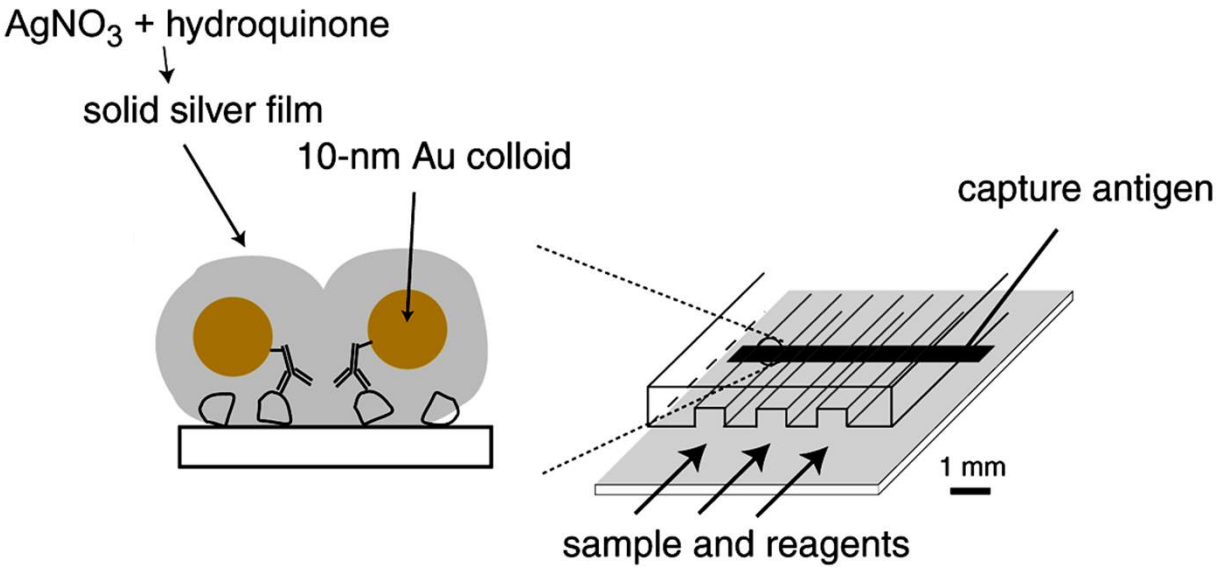






Linder, Sia, and Whitesides, *Anal. Chem.*, 77:64 (2005)

Silver reduction enables the use of microfluidics

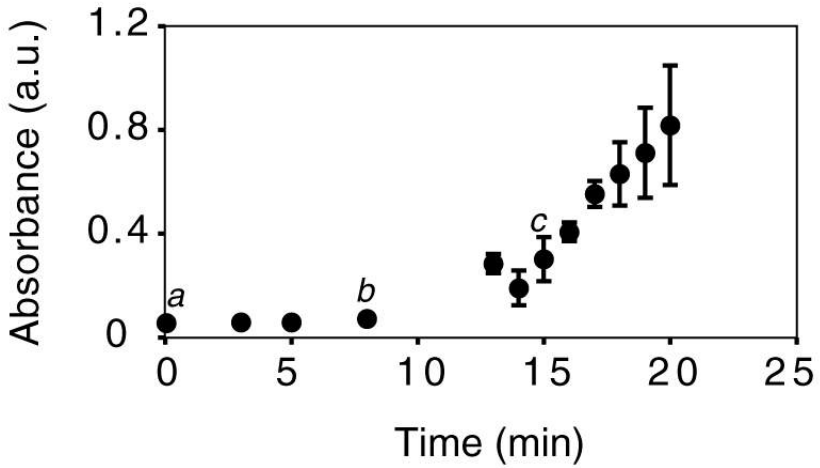


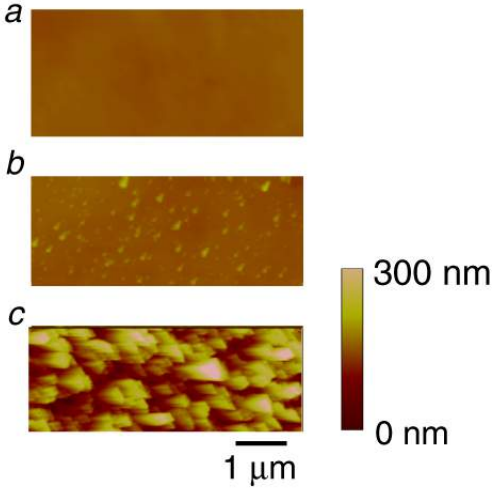
An Integrated Approach to a Portable and Low-Cost Immunoassay for Resource-Poor Settings**

*Samuel K. Sia, Vincent Linder, Babak Amir Parviz, Adam Siegel, and George M. Whitesides**

The development of technology for use in resource-poor countries encounters a specific type of challenge not ordinarily faced in academic science: the technology must be inexpensive and it must work with minimal infrastructure.

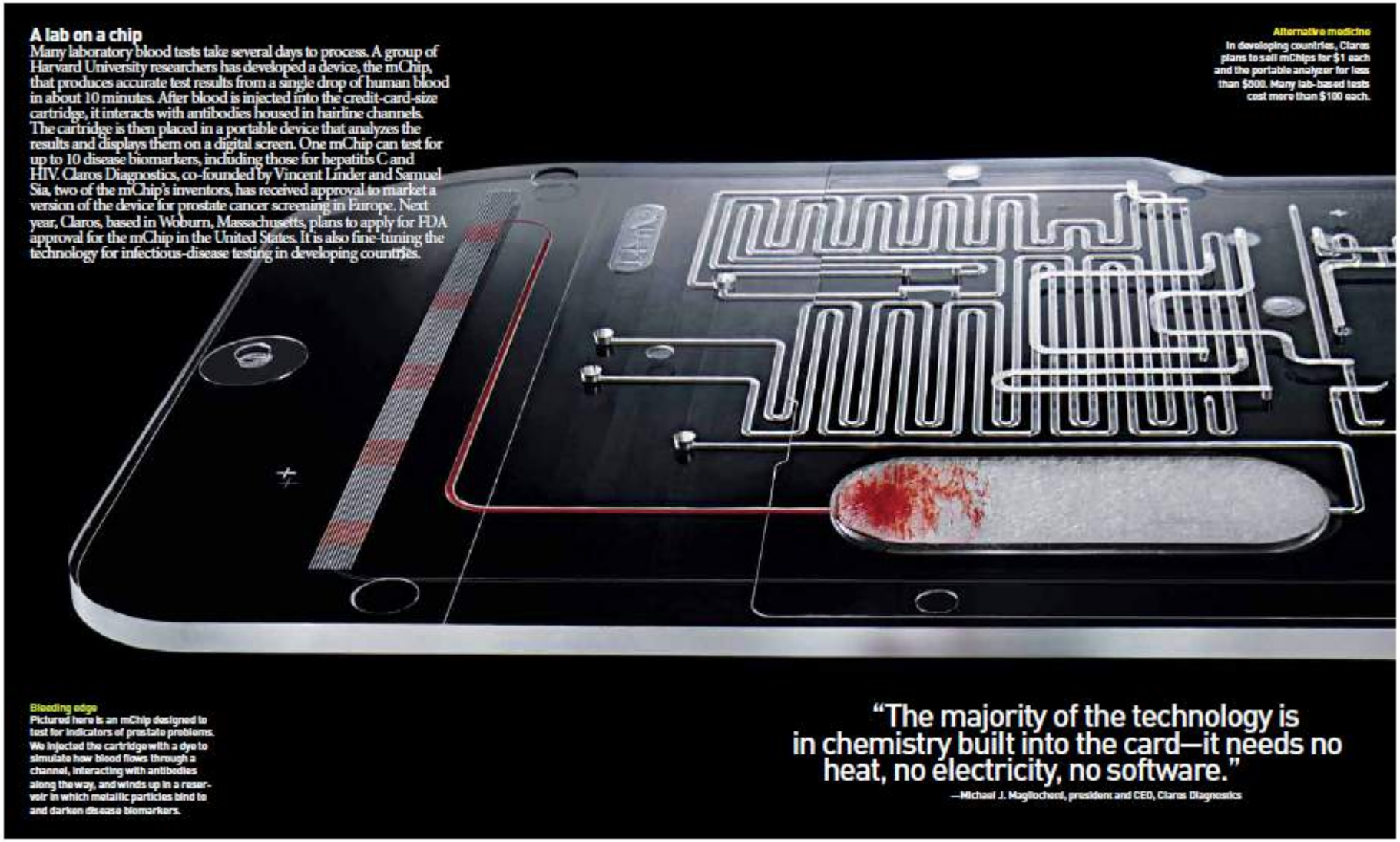
Angew Chemie, 43:498 (2004)





A lab on a chip

Many laboratory blood tests take several days to process. A group of Harvard University researchers has developed a device, the mChip, that produces accurate test results from a single drop of human blood in about 10 minutes. After blood is injected into the credit-card-size cartridge, it interacts with antibodies housed in hairline channels. The cartridge is then placed in a portable device that analyzes the results and displays them on a digital screen. One mChip can test for up to 10 disease biomarkers, including those for hepatitis C and HIV. Claros Diagnostics, co-founded by Vincent Linder and Samuel Sia, two of the mChip's inventors, has received approval to market a version of the device for prostate cancer screening in Europe. Next year, Claros, based in Woburn, Massachusetts, plans to apply for FDA approval for the mChip in the United States. It is also fine-tuning the technology for infectious-disease testing in developing countries.



Alternative medicine
In developing countries, Claros plans to sell mChips for $1 each and the portable analyzer for less than $800. Many lab-based tests cost more than $100 each.

Bleeding edge
Pictured here is an mChip designed to test for indicators of prostate problems. We injected the cartridge with a dye to simulate how blood flows through a channel, interacting with antibodies along the way, and winds up in a reservoir in which metallic particles bind to and darken disease biomarkers.

"The majority of the technology is in chemistry built into the card—it needs no heat, no electricity, no software."

—Michael J. Maglichetti, president and CEO, Claros Diagnostics

PHOTOGRAPH BY **NIGEL COX** | REPORTED BY **CHRISTINE LAGORIO**

	ELISA	mChip
signal generation	enzyme/substrate reaction	silver precipitation *(photography)*
light source	lasers, lenses, filters	LEDs *(ambient lighting)*
detector	photomultiplier tubes	photodetector *(photocopier)*
manufacturing	plastic 96-well plates	injection-molded plastic *(consumer toys)*

Claros Diagnostics

Point-of-care ELISA

Founded in 2004 (with Vincent Linder and David Steinmiller), based in Boston area

raised ~$12M in VC funding

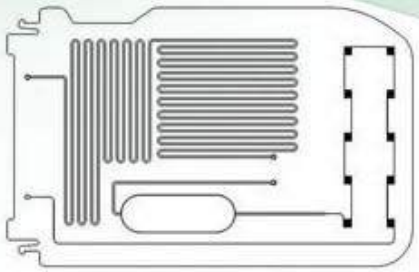
First product: prostate cancer monitoring

ISO-certified manufacturing facility and clean room

approved in Europe (CE Mark)

acquired by Opko Health in 2011 (~$50M)

awaiting FDA approval and launch of PSA test and eventually 4K panel (total PSA, free PSA, intact PSA, HK2)



PRODUCTS OVERVIEW

OPKO DIAGNOSTICS SYSTEM

Hardware Device

Total PSA Test

4Kscore™ Prostate Cancer Test

Vitamin D Test

Testosterone Test

Alzheimer's Disease Tests

OPKO CHILE

OPKO EU

OPKO FINETECH

OPKO Diagnostics Point-of-Care System

OPKO Diagnostics is transitioning in-vitro medical diagnostic tests from the laboratory to the point-of-care, such as physicians' offices, patients' homes, and emergency settings. This novel point-of-care system includes the following elements:

Tests Under Development:

- Prostate-Specific Antigen (Total PSA) Test
- 4KScore™ Prostate Cancer Test
- Vitamin D Test
- Testosterone Test
- Alzheimer's Disease Test

Hardware System:

OPKO's point-of-care hardware system consists of a disposable, microfluidic test cassette and a robust, compact analyzer. This device is able to produce laboratory-quality test results from a single finger-stick of blood in about 10 minutes.

technology review
Published by MIT

The Year's Best Tech Products

A roundup of the most significant technologies to come to market in 2010.

The 50 Most Innovative Companies 2011

Clinical scenario

Pregnant woman in high burden-of-disease area
(health clinic in U.S. inner city, village in sub-Saharan Africa)

Healthcare professional sees this patient for the first time:
no patient records

No lab testing available

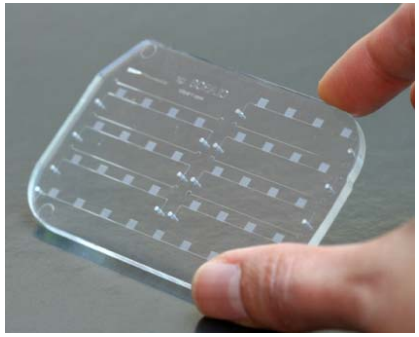
Symptoms:
fever, pain, sore throat, weight loss, headache

Traditional response

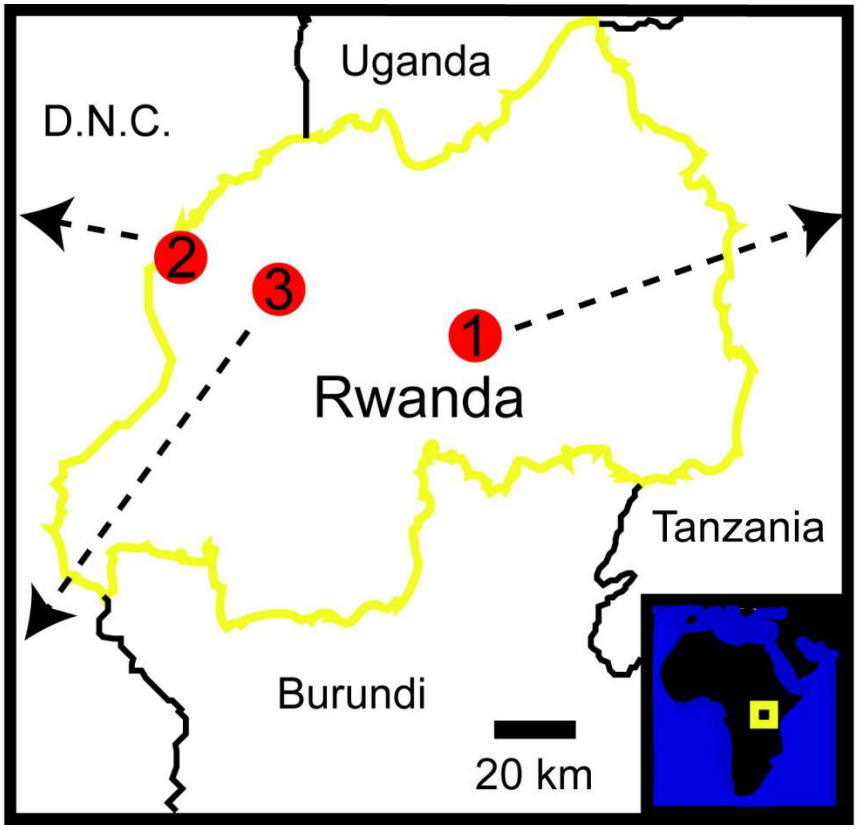
manage based only on symptoms
(syndromic management)

New response

precision diagnosis



Columbia ICAP testing sites (School of Public Health)



Test sites:

1. Kigali (national testing center)
2. Gisenyi (regional testing center)
3. Kabaya (rural health clinic)

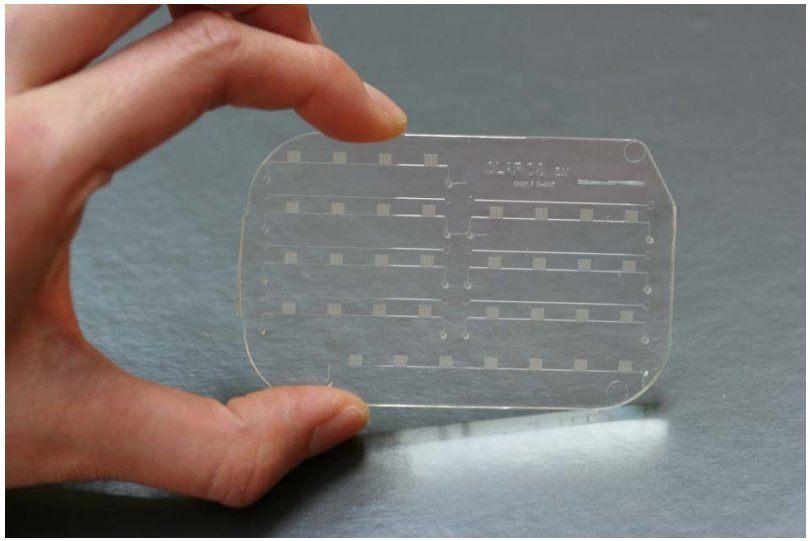
TECHNICAL REPORTS

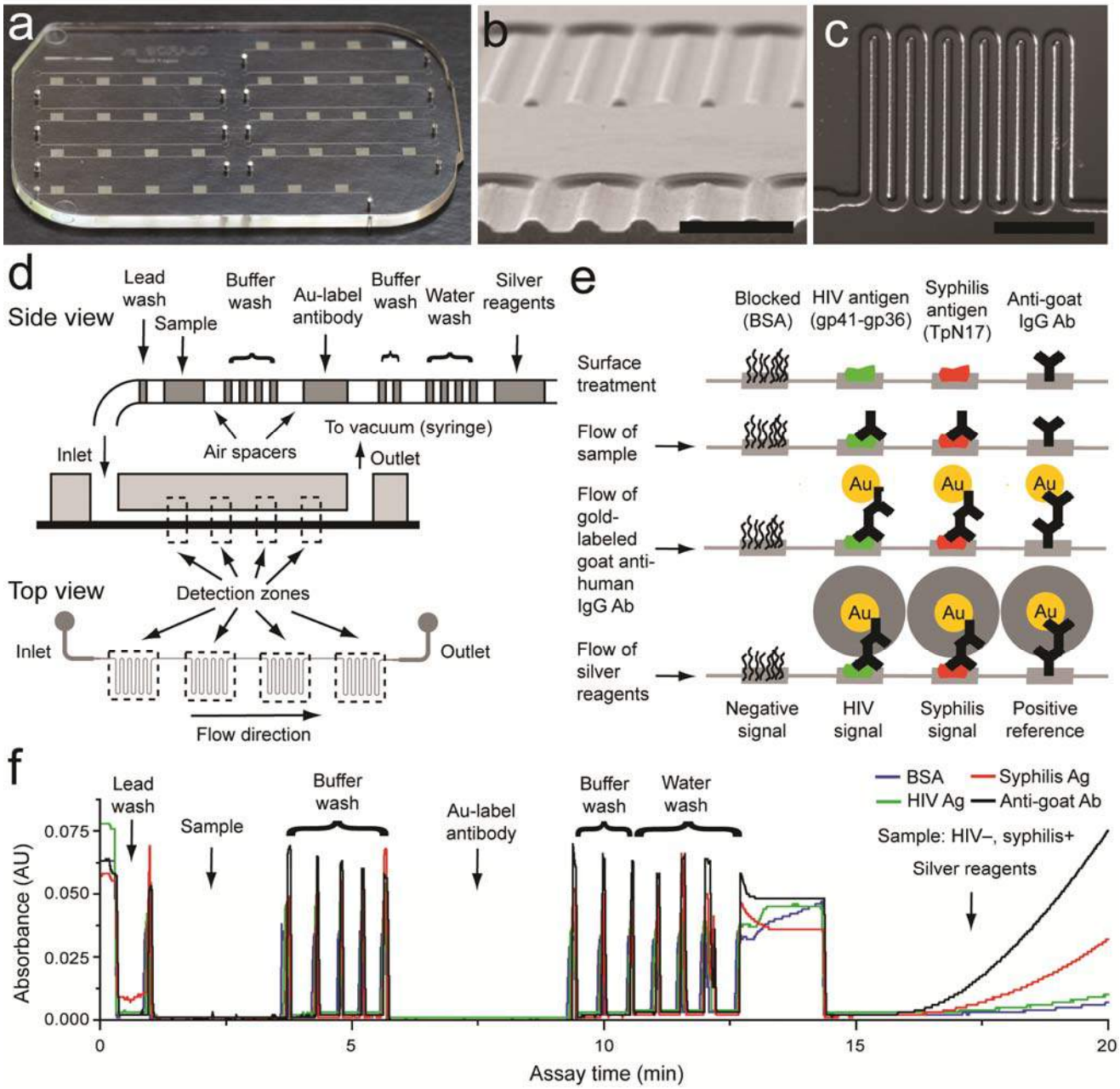
nature medicine

Microfluidics-based diagnostics of infectious diseases in the developing world

Curtis D Chin[1], Tassaneewan Laksanasopin[1], Yuk Kee Cheung[1], David Steinmiller[2], Vincent Linder[2], Hesam Parsa[1], Jennifer Wang[1], Hannah Moore[1], Robert Rouse[1], Gisele Umviligihozo[3], Etienne Karita[3], Lambert Mwamarangwe[4], Sarah Braunstein[5], Janneke van de Wijgert[4,6], Ruben Sahabo[5], Jessica Justman[5], Wafaa El-Sadr[5] & Samuel K Sia[1]

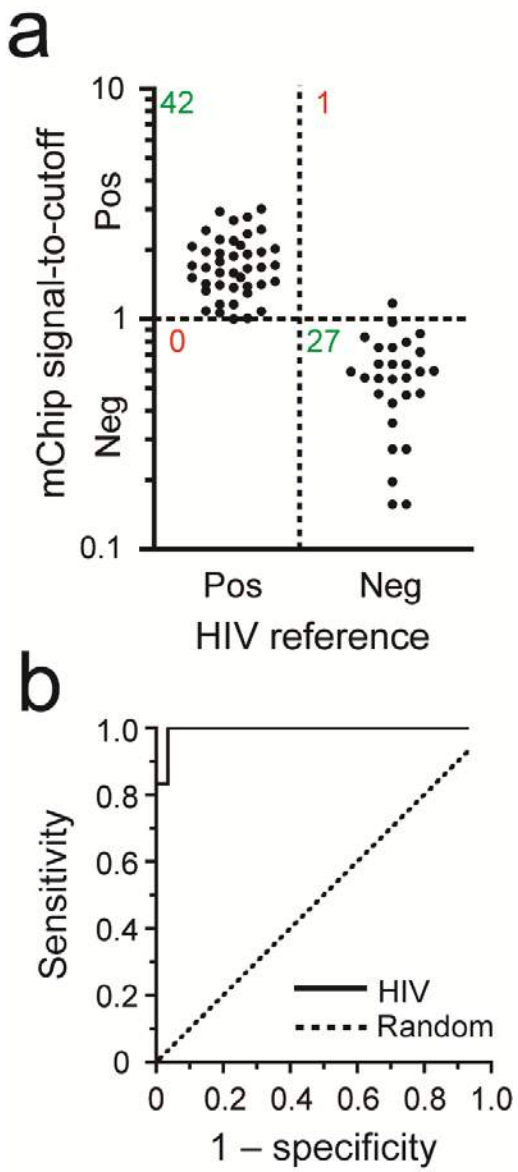
August 2011





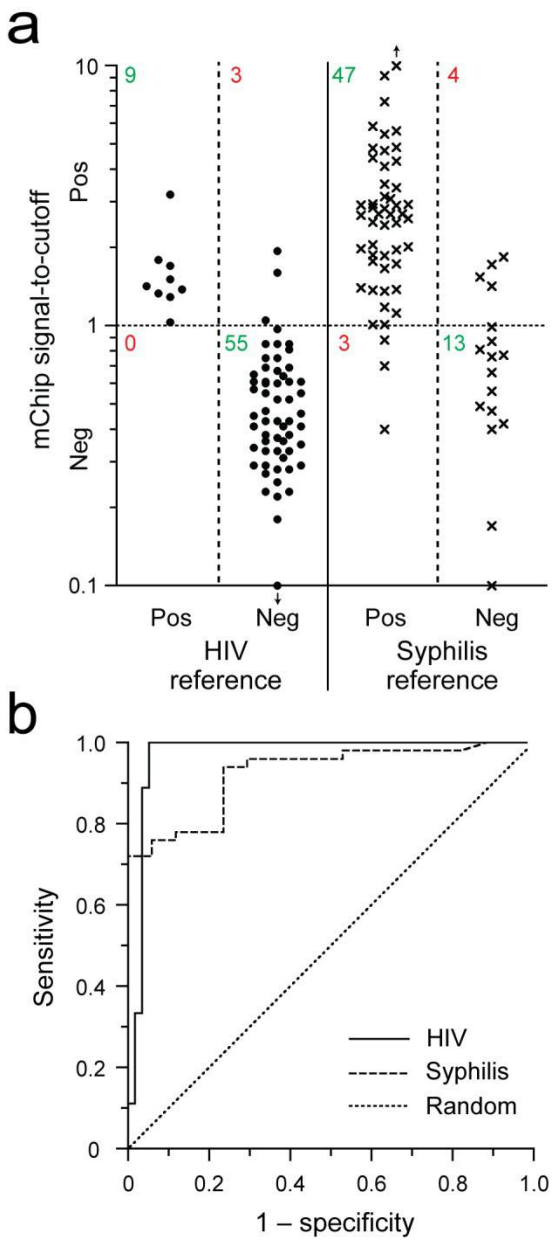
Chin et al, Nature Medicine, August 2011

Rwanda: 1 uL of whole blood



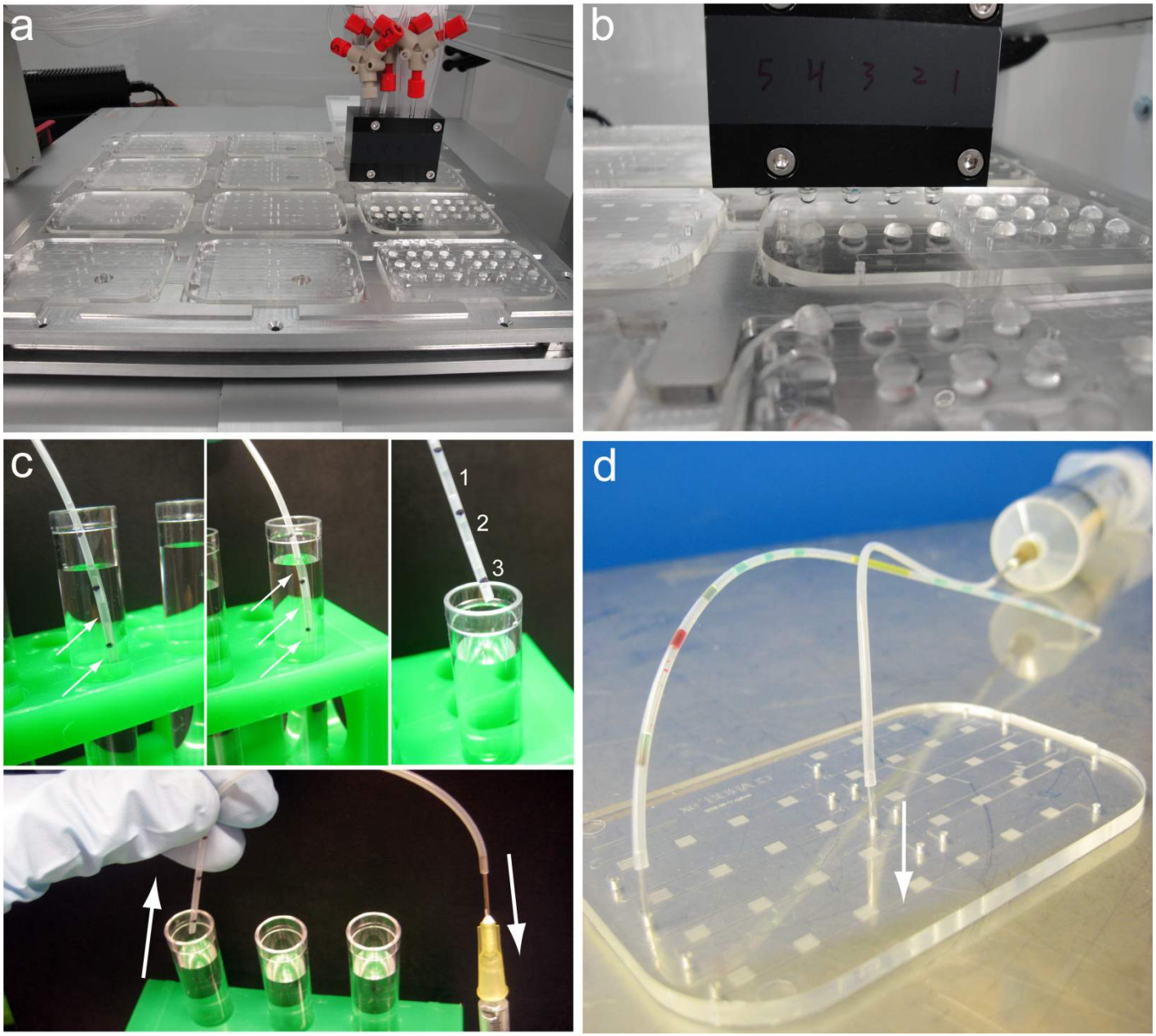
Chin et al, Nature Medicine, August 2011

Rwanda: 7 uL of plasma/sera



Chin et al, Nature Medicine, August 2011

Scale-up in manufacturing



WALL STREET JOURNAL

October 17, 2011

Columbia University and **Claros Diagnostics** Inc., U.S.: A low-cost hand-held device that can diagnose multiple infectious diseases from a drop of a patient's blood. It is designed to be used in poor and remote parts of the world.

The Washington Post

August 1, 2011

New device could streamline HIV testing

First trial in Rwanda for 'lab on a chip' a success in detecting infections

BY CHRISTIAN TORRES

The first field trial of a "lab on a chip" accurately detected both HIV and syphilis among a Rwandan population, researchers reported Sunday.

Blood samples injected into the clear plastic, credit card-shaped device produced results within 20 minutes. This kind of test could offer a faster, cheaper and easier way to detect infectious diseases that afflict developing countries, according to the report published online by Nature Medicine.

"This is a big step," said Doris Rouse, a vice president at RTI International in North Carolina, who specializes in global health technologies and was not involved with the study. "What's especially exciting about this device is that it's rugged, easy to use and doesn't require a lot of infrastructure or training," she added.

Cheap HIV tests that provide results within 30 minutes have been available for years, but many rely on a method called lateral flow. A sample of blood or oral fluid is placed on a strip of paper, and like a pregnancy test, a colored band appears and can be interpreted to indicate infection.

Few lateral flow tests, however, have proven reliable across multiple settings and types of infection. Many people in developing countries instead rely on expensive and time-consuming laboratory analysis, "but this [new] test can be done outside the lab with all the same advantages and sensitivity [for detection,]" said Rosanna Peeling, a diagnostics researcher at the London School of Hygeine and Tropical Medicine, who was not part of the study.

The lab on a chip trial shows 100-percent detection of HIV-positive cases, with only one false positive out of 70 total samples, according to the report. When a dual test of HIV and syphilis was performed, the chip had similar accuracy for HIV; 94 percent of syphilis cases were detected, though there was a higher rate — four out of 67 total samples — for false positives.

Overall, the test proved successful in a difficult environment with little infrastructure, said Samuel Sia, one of the study's authors and a biomedical engineer at Columbia University. "We've taken what's long been a great theoretical concept and shown that it can be done in the field," he added.

Sia tested the device in Rwanda, where about 3 percent of the adult population is infected with HIV, according to the World Health Organization. Currently, patients in the city of Kigali have to provide blood at the local hospital, which sends samples to a national laboratory for analysis.

Turnaround time for results could be days or weeks, but the chip, which can be used at the hospital, detected HIV and syphilis within 20 minutes.

According to Sia, the chip could also potentially detect hepatitis B and C, herpes, gonorrhea and chlamydia — infections that are often found in combination with HIV and have few reliable and cheap tests available. All infections could be detected on a single device, at the same time and with a small amount of blood — a fraction of a needle prick's worth.

The chip, which the research team named mChip, is comparable in price to lateral flow tests. Sia estimated his device would cost about $2 to $3; lateral flow tests can cost more than $4 and lack the cost-efficiency of detecting multiple infections. Most lateral flow tests also require interpretation, but Sia is developing a reading device — much like an ATM for the credit card-sized lab on a chip — that can provide an easy, yes-or-no diagnosis within seconds.

Gottfried Hirnschall, director of the WHO HIV/AIDS department, wrote in an e-mail that the organization "welcomes this development," adding that these devices "will be particularly useful" in eliminating transmission of HIV and syphilis from mother to child through earlier treatment.

Shiva Goudar, a researcher at Jawaharlal Nehru Medical College in Belgaum, India, helps test for HIV among local pregnant women. He said many patients live two or three hours away from the hospital centers where blood samples are collected, and it can take two days to receive results.

The lab on a chip could be used by primary-care providers within the same village, Goudar said, and "doing this test at the point of care cuts down on the time, effort and logistics of transport for the blood sample." It would provide a "tremendous advantage" over the current testing practice.

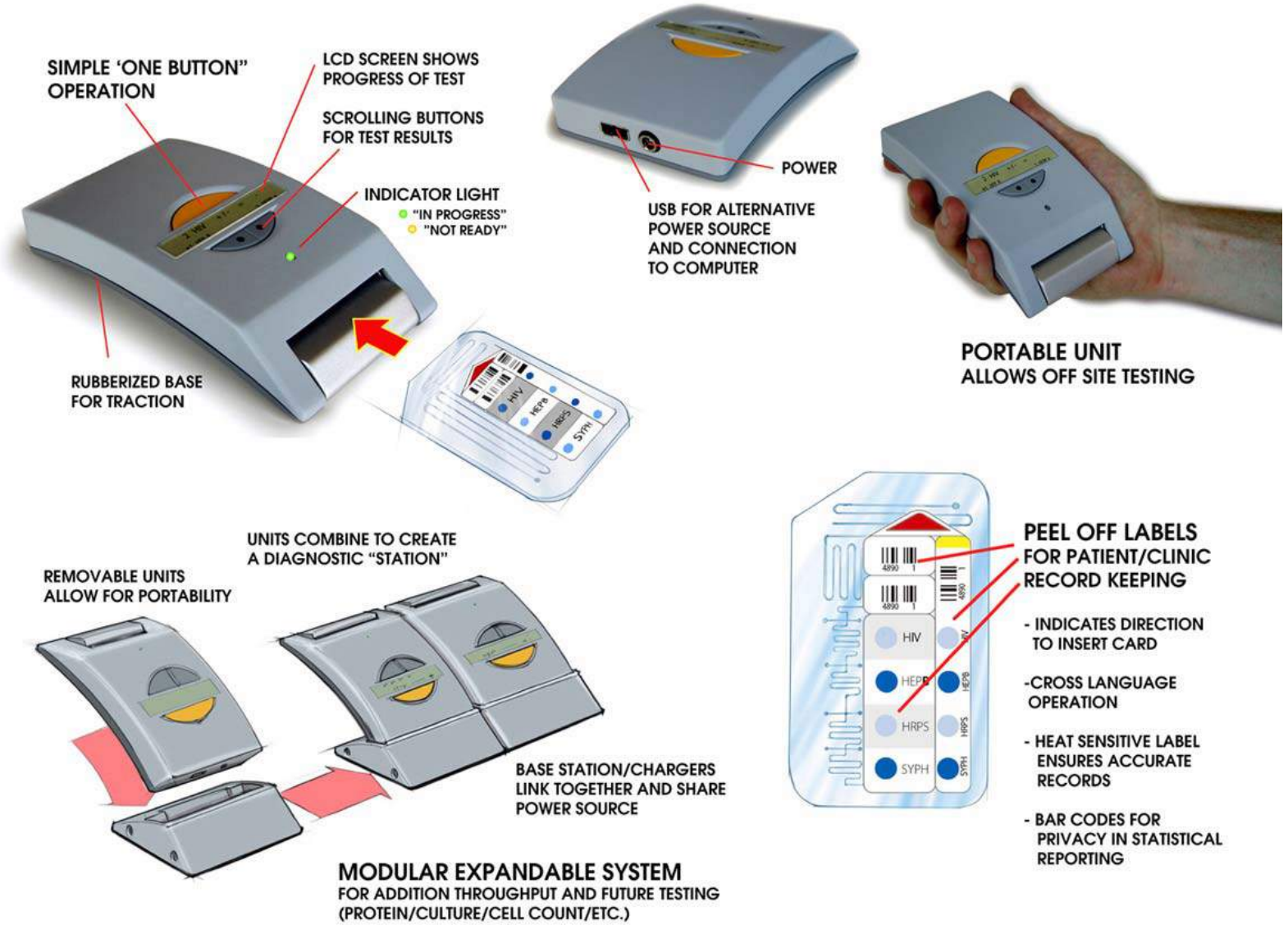
Sia presented the chip test at a technology competition for maternal and child health last week in Washington. Sponsored by USAID, the Gates Foundation and others, the "Saving Lives at Birth" challenge will award a total of $14 million to relevant projects. Sia's lab on a chip is one of 18 nominees for a number of grants to be awarded by the end of 2011.

Funding is crucial for further development of the lab on a chip. A lack of interest from companies is likely keeping the test from reaching the ground within two or three years, Sia estimated, despite excitement from the global health community. "The challenge now," he added, "is how to go from an academic study to distributing this test in the field."

torresc@washpost.com

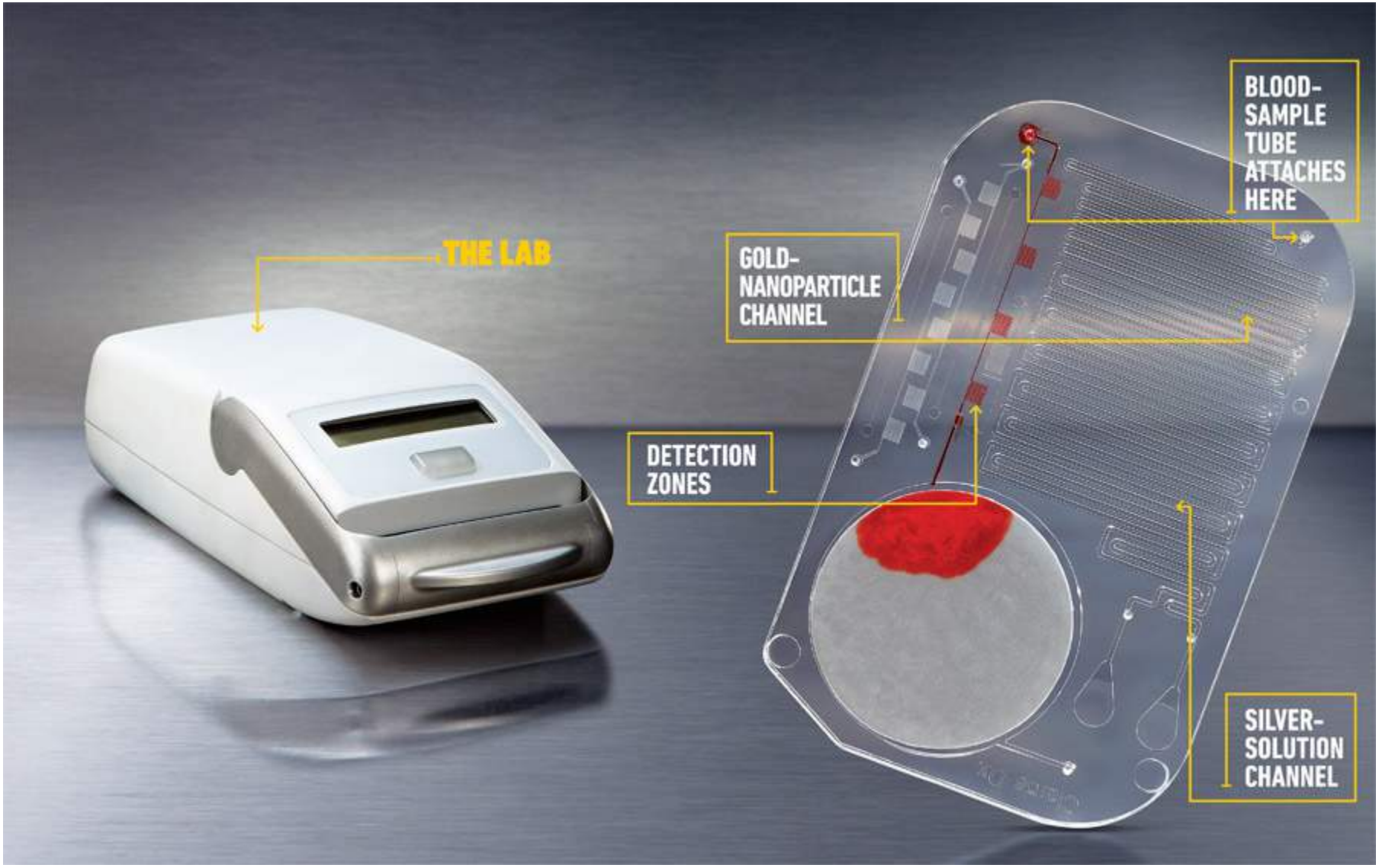
nature.com

Design of a mobile device



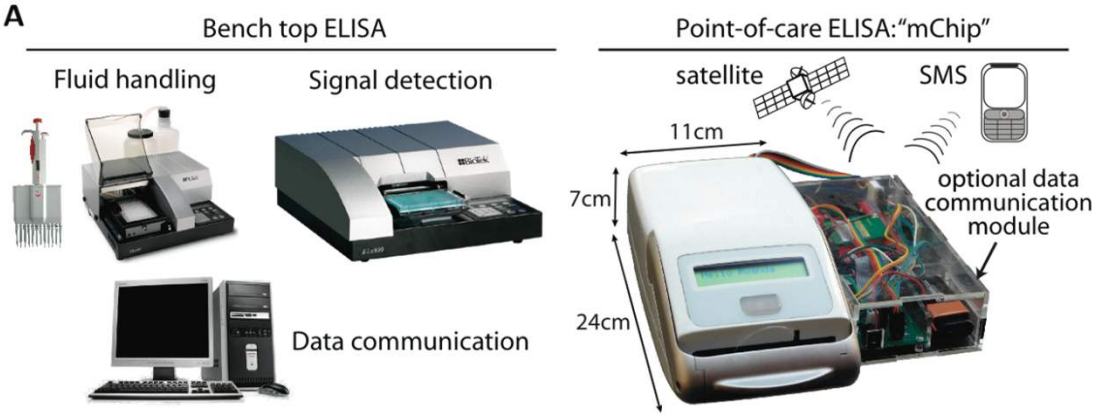
Pratt Design Incubator for Sustainable/Social Enterprise

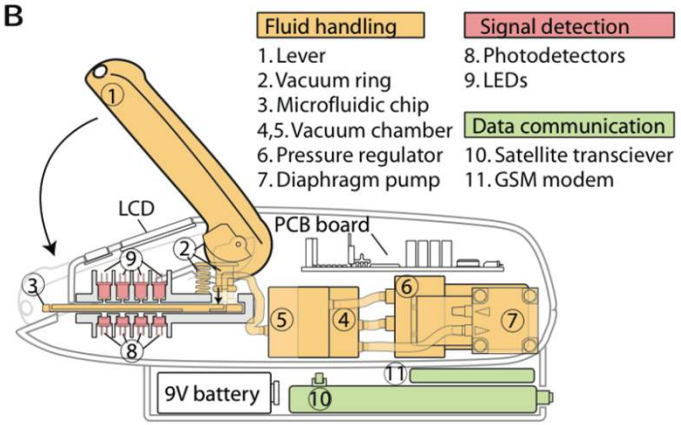
SMART DESIGN

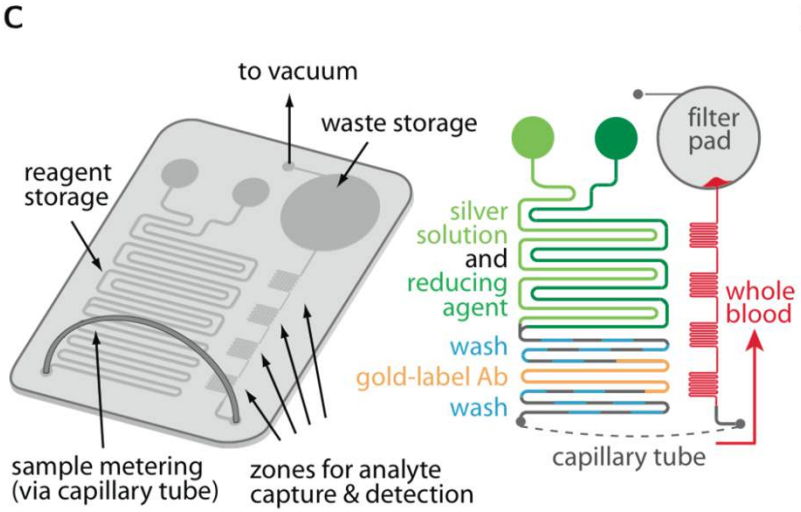


Popular Science, 2010

Mobile device for disease diagnosis and data-tracking in resource-limited settings







D

	Benchtop ELISA				mChip
	liquid ‡ handling	signal # detection	data processing & ^ communication	total	total
Space (in³)	2380	2170	1170	5720	180
Power (W)	150	300	50	500	0.6
Cost (USD)	$9,600	$8,850	$1,000	$19,450	< $800*
Reagent volume / test (µL)	4400†				160
Sample volume / test (µL)	75†				0.2
Time to run assay (min)	130†				20
Time from sample collection to results (min)	150				20
Objective interpretation of results	Yes				Yes
Handles whole blood	No				Yes

‡ Biotek Microplate Washer ELx405 # Biotek Microplate Reader ELx808 ^ Dell Latitude E6400
† Bio-Rad Genetic Systems HIV-1/HIV-2 PLUS O Enzyme Immunoassay (FDA-approved)
* estimated manufacturing cost

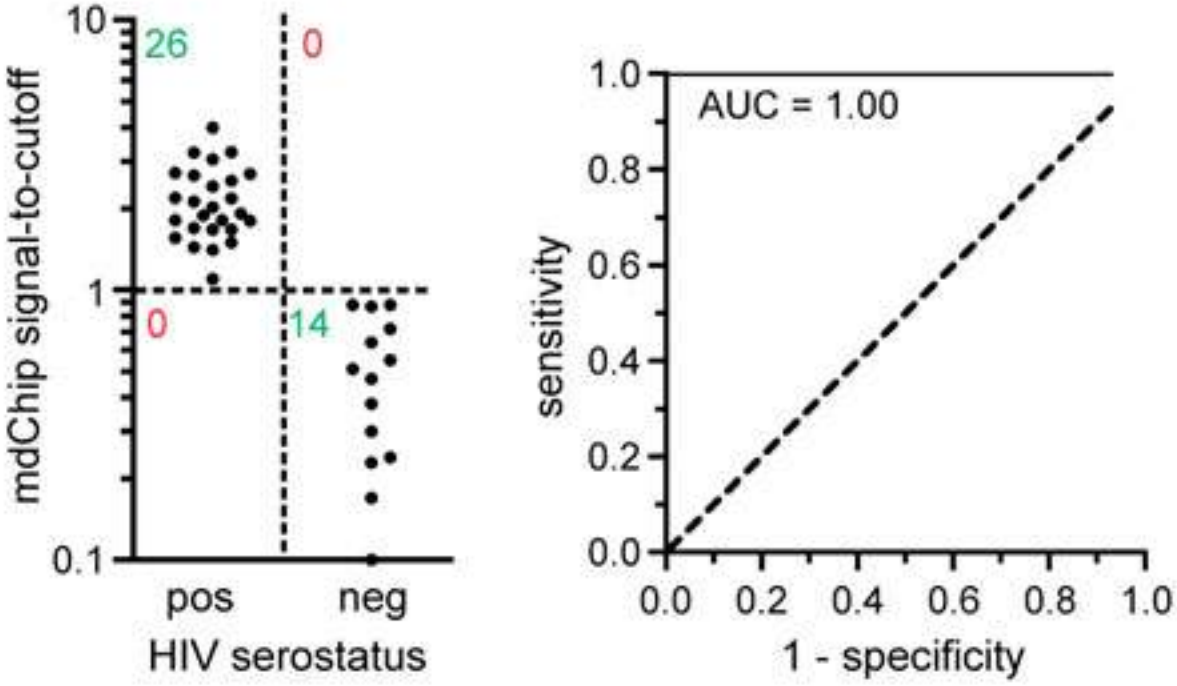
Chin et al, Clin. Chem., 59:4, 2013

seamless integration with patient records

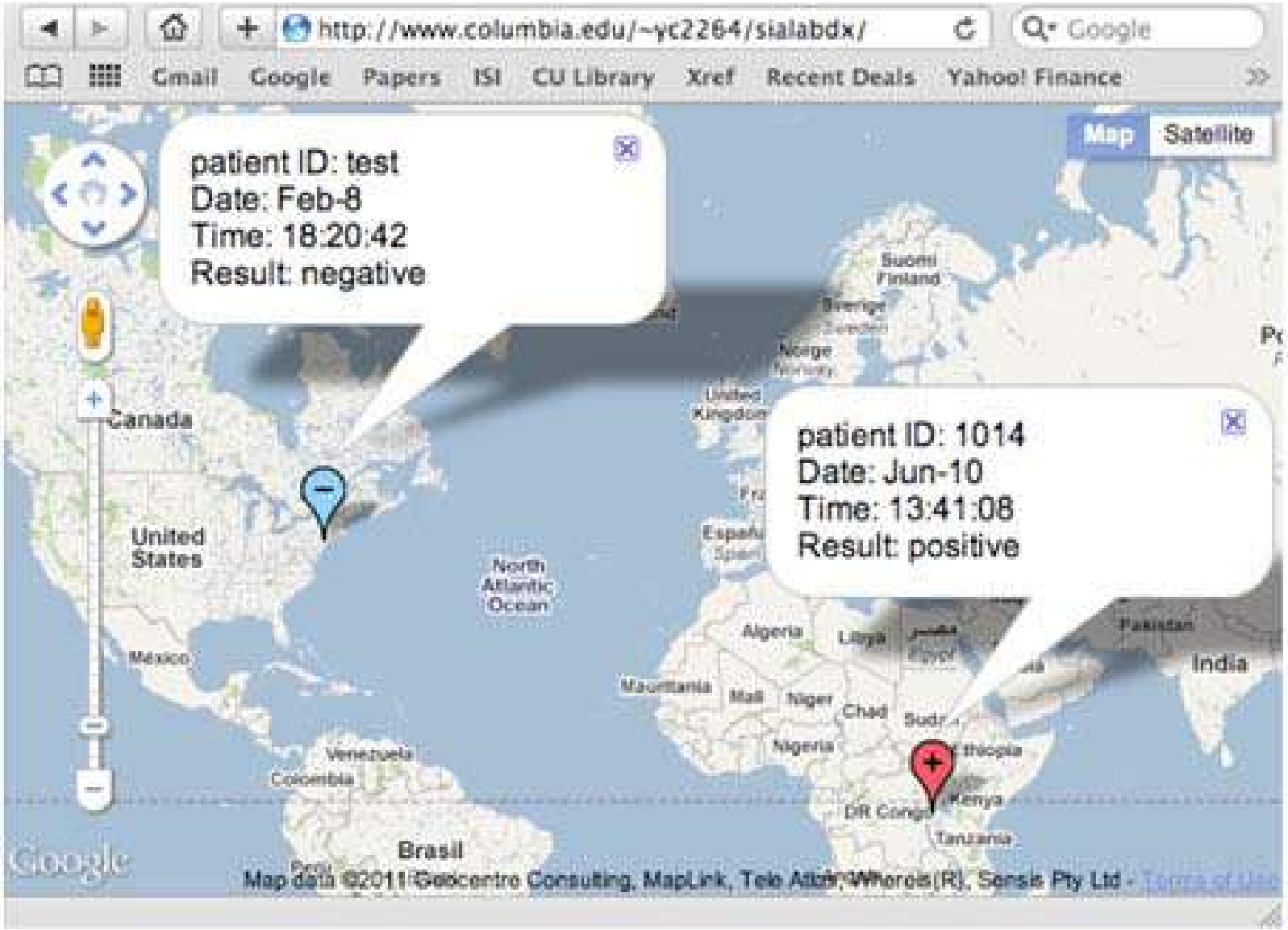
time stamp, geotagged diagnostics results

secure data transmission

Whole-blood analysis...

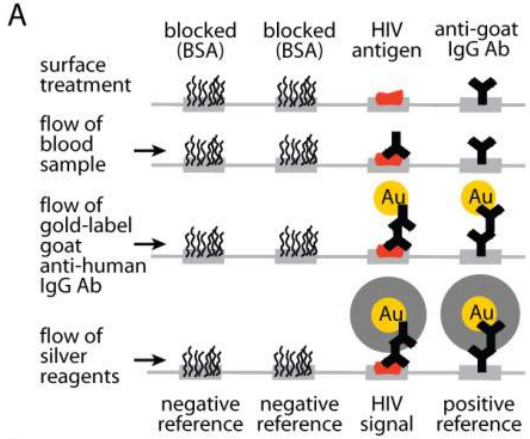


...with real-time surveillance of diseases

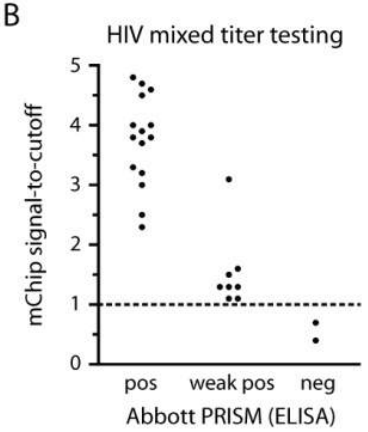


Head-to-head with lateral flow tests: commercial plasma panel with low and high antibody titers

A



B



C

sample	mChip (signal-to-cutoff)	Abbott PRISM HIV O+ ELISA (signal-to-cutoff)	HIV rapid tests				
			Abbott Deter-mine	Murex SUDS	OraSure Oraquick	MedMira Reveal	Trinity Biotech Uni-gold
PRB204-01	weak pos (1.3)	weak pos (1.2)	neg	neg	neg	neg	neg
PRB204-02	pos (3.9)	pos (118.3)	pos	pos	pos	pos	pos
PRB204-03	neg (0.4)	neg (0.5)	neg	neg	neg	neg	neg
PRB204-04	pos (4.5)	pos (80.8)	pos	pos	pos	pos	pos
PRB204-05	pos (3.0)	pos (128.3)	pos	pos	pos	pos	pos
PRB204-06	pos (2.5)	pos (107.6)	pos	pos	pos	pos	pos
PRB204-07	pos (4.8)	pos (135.8)	pos	pos	pos	pos	pos
PRB204-08	pos (3.8)	pos (133.9)	pos	pos	pos	pos	pos
PRB204-09	weak pos (1.3)	weak pos (2.4)	neg	neg	neg	neg	neg
PRB204-10	pos (2.3)	pos (21.5)	pos	neg	neg	neg	neg
PRB204-11	pos (3.8)	pos (141.8)	pos	pos	pos	pos	pos
PRB204-12	pos (4.0)	pos (76.1)	pos	pos	pos	pos	pos
PRB204-13	weak pos (1.5)	weak pos (15.2)	pos	pos	ind	pos	neg
PRB204-14	pos (4.6)	pos (122.3)	pos	pos	pos	pos	pos
PRB204-15	pos (3.7)	pos (121.8)	pos	pos	pos	pos	pos
PRB204-16	pos (3.3)	pos (22.8)	pos	pos	pos	pos	pos
PRB204-17	pos (3.2)	pos (28.8)	pos	pos	pos	pos	pos
PRB204-18	weak pos (1.1)	weak pos (11.0)	pos	neg	ind	pos	neg
PRB204-19	weak pos (1.1)	weak pos (5.1)	pos	pos	pos	pos	neg
PRB204-20	pos (4.0)	pos (119.1)	pos	pos	pos	pos	pos
PRB204-21	pos (3.1)	weak pos (6.5)	pos	pos	pos	pos	neg
PRB204-22	pos (4.7)	pos (123.1)	pos	pos	pos	pos	pos
PRB204-23	neg (0.7)	neg (0.3)	neg	neg	neg	neg	neg
PRB204-24	weak pos (1.6)	weak pos (4.6)	pos	neg	neg	neg	neg
PRB204-25	weak pos (1.3)	weak pos (7.4)	pos	neg	pos	neg	pos

different result than Abbott ELISA

"Timely and accurate insight on current and emerging risks": Network of sensors integrated with the cloud

- maintain a global health perspective
- strengthen partnerships

Clinical Chemistry 59:4
589–591 (2013)

Editorials

fast track

A Glimpse into the Future of Diagnostics

George M. Whitesides*

In this issue of *Clinical Chemistry*, a report by the teams of Sam Sia (at Columbia) and Vincent Linder (at Claros/OPKO), together with a large group of collaborators, provides a remarkable example of what happens when one rethinks, both creatively and practically, how to collect diagnostic information in the developing world *(1)*. By combining innovative engineering, a mixture of new and familiar technologies, good design, and careful attention to limited resources (human, financial, energetic), they have produced an integrated system whose impressive capabilities suggest a new approach to the design of portable diagnostic systems.

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Energy & Sustainability :: Fast Company :: February 5, 2013 :: Email :: Print

A Mobile Device That Diagnoses STDs On The Spot With A Simple Finger Prick

To help curb HIV in the developing world, doctors need to be able to quickly find out who needs to be treated without waiting weeks for samples to be taken to the nearest hospital.

FAST COMPANY

By Ariel Schwartz

A MOBILE DEVICE THAT DIAGNOSES STDS ON THE SPOT WITH A SIMPLE FINGER PRICK

To help curb HIV in the developing world, doctors need to be able to quickly find out who needs to be treated without waiting weeks for samples to be taken to the nearest hospital. The mChip does that, using just

NATURE MEDICINE | SPOONFUL OF MEDICINE

Blue-sky HIV test chip will upload results to the cloud

28 Jan 2013 | 13:54 EST | Posted by Yevgeniy Grigoryev | Category: AIDS

In Rwanda, the most densely populated country in Africa, there are approximately 190,000 people living with HIV, with electronic records facilitating care for over 90,000 of them. However, many thousands of HIV-infected people there who don't have access to health centers remain undiagnosed.

It's exactly this type of situation that Samuel Sia hopes to ameliorate. Sia, a biomedical engineer, and his team at Columbia University in New York have combined the portability of mobile technology with the detection potential of enzyme-linked antibodies to create a fully automated and portable microfluidic device dubbed the 'mChip'. The scientists tested the device on serum, plasma and blood samples from over 200 HIV-infected individuals in Rwanda and published their findings in this month's issue of *Clinical Chemistry*.

The device uses blood from a finger prick, similar to that employed by a glucose meter, which is automatically loaded onto a small fluidics chip that

Claros Diagnostics

ICAP
International Center for AIDS Care and Treatment Programs
MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University

REPUBLIC OF RWANDA
MINISTRY OF HEALTH

amc
ACADEMIC MEDICAL CENTER OF
THE UNIVERSITY OF AMSTERDAM

Projet Ubuzima

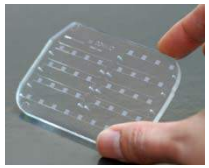
SMART DESIGN

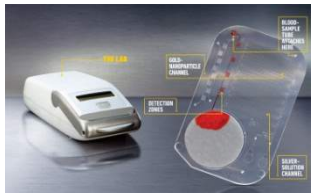
PrattDesign Incubator
for Sustainable Innovation

Commons Capital
Venture Capital for a Sustainable Future

RTI INTERNATIONAL

Product evolution of mChip technology





	Reference lab test - ELISA	Claros Diagnostics	mChip (not automated)	mChip device
Year started	1970's	2002	2005	2008
Automation	yes	yes	no	yes
Specimen	venipuncture	finger-prick	finger-prick	finger-prick
Speed	3 hours	15 min	15 min	15 min
Accuracy	high	same as ELISA	same as ELISA	same as ELISA
Device Cost	$100,000	$3000	--	$200
Disposable COGS	~$1	$2	$2	$2
Target	proteins	proteins (PSA)	proteins (HIV, STDs)	proteins (HIV, STDs)
Reference Publications	many	(awards: 2010 MIT Tech.Review, 2011 WSJ Innovation)	Chin et al, Nature Med, 2011	Chin et al, Clin Chem, 2013

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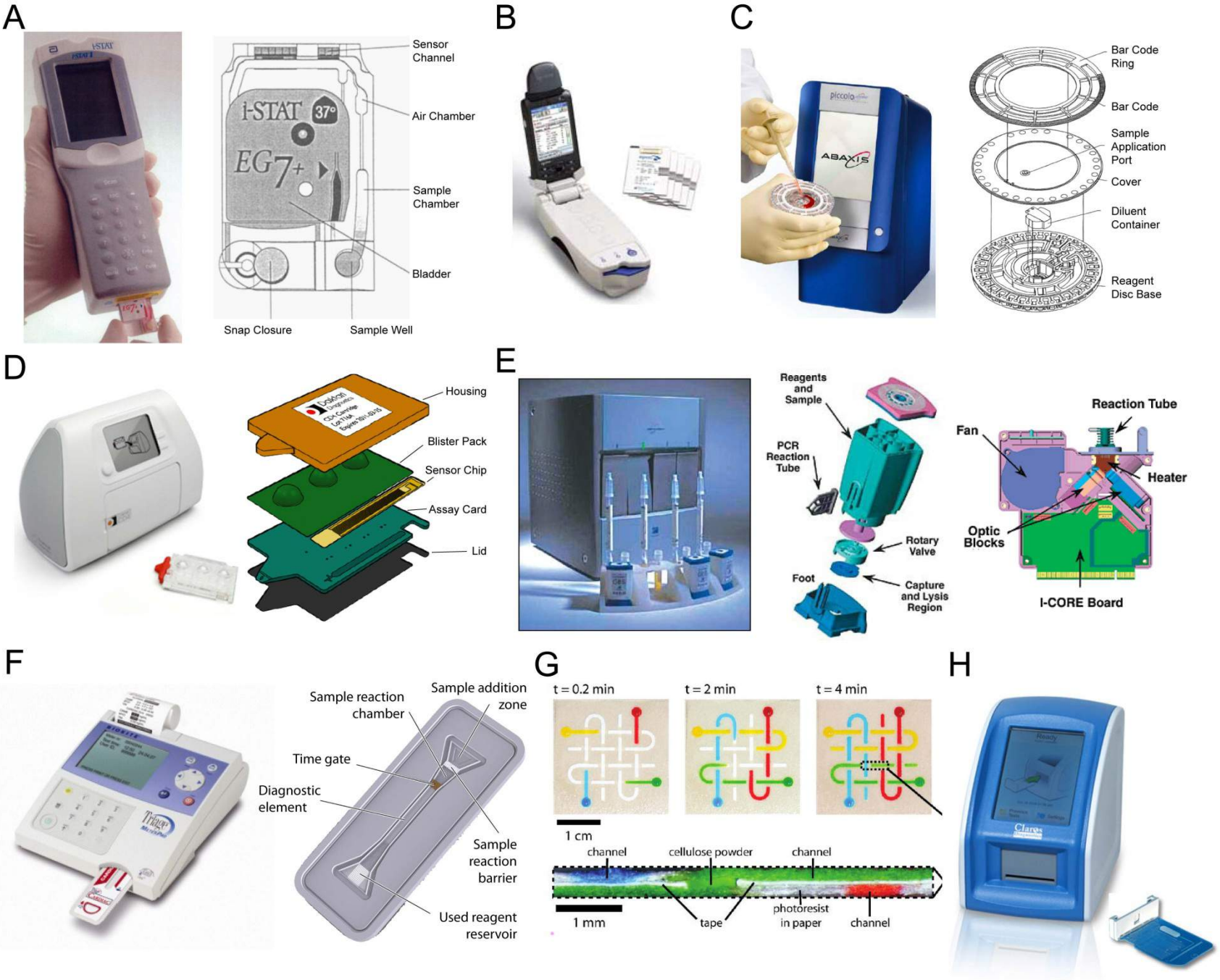
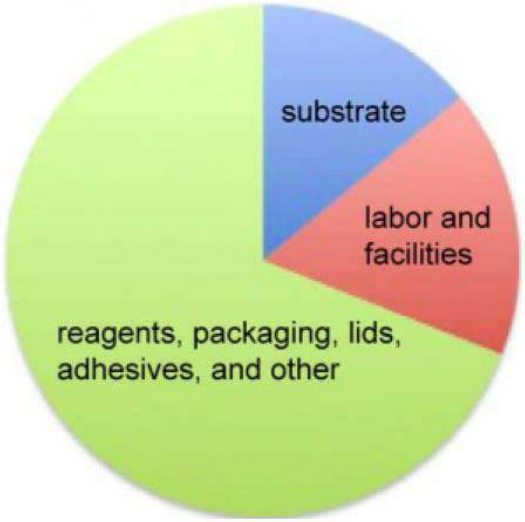


Chin, Linder, and Sia, "Commercialization of microfluidic point-of-care diagnostic devices", Lab Chip, 2012

Approximate cost breakdown of Claros plastic microfluidics cartridge



Market prices of HIV lateral flow tests

HIV rapid test	Manufacturer	Price (US$)
Capillus	Trinity Biotech	2.20
Determine	Abbott Diagnostics	1.20
First Response	Premier Medical Corp	1.15
OraQuick	OraSure Technologies	4.00
SD Bioline	Standard Diagnostics	1.10
Uni-Gold	Trinity Biotech	2.34

Chin, Linder, and Sia (Lab Chip, 2012)

Large public health impact
Extremely cost-effective

Projected Benefits and Costs	Rwanda	Tanzania	India
Syphilis - screening and treating infected pregnant women with single dose of penicillin			
Deaths avoided (by preventing congenital syphilis, low birth weight, and stillbirths)	3,436	2,140	84,023
DALYs avoided (by preventing congenital syphilis, low birth weight, and stillbirths)	125,015	77,832	3,056,052
Deaths avoided (by intervening progression to tertiary syphilis)	1,612	1,441	78,913
DALYs avoided (by intervening progression to tertiary syphilis)	88,444	55,375	2,173,337
Present value (annual treatment costs avoided)	1,223	700	30,048
Present value (annual incremental costs of testing)	569,047	1,906,847	40,290,769
HIV			
Present value (annual incremental costs of testing)	-$65,508	-$220,237	-$4,638,253
Total			
Deaths avoided	5,048	3,581	162,936
DALYs avoided	213,459	133,207	5,229,389
Present value (annual treatment costs avoided)	$1,223	$700	$30,048
Present value (annual incremental costs of testing)	$503,539	$1,686,610	$35,652,516
Cost/DALY avoided	**$2.35**	**$12.66**	**$6.81**
GDP per capita (2012–2016)	**$419–$479**	**$517–$620**	**$1,497–$2,002**

reference cost/DALY: $1000-$5000 (immunization), $1000 (ORT), $1000 (water and sanitation) (source: DCPP)

source: RTI and Commons Capital
analysis funded by Gates Foundation

What's in store for global health diagnostics?

Technology challenges:

- Device integration
- User experience

Business challenges:

- Revenue: first-world markets
- Cost: re-think target product profiles *(Buffett rule)*

New resources in 2014 (vs. 2004):

- Tech revolution in hardware and software

Acknowledgments – Sia Lab

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