Reaching the Hard-to-Reach Populations in Infectious Disease Diagnostics

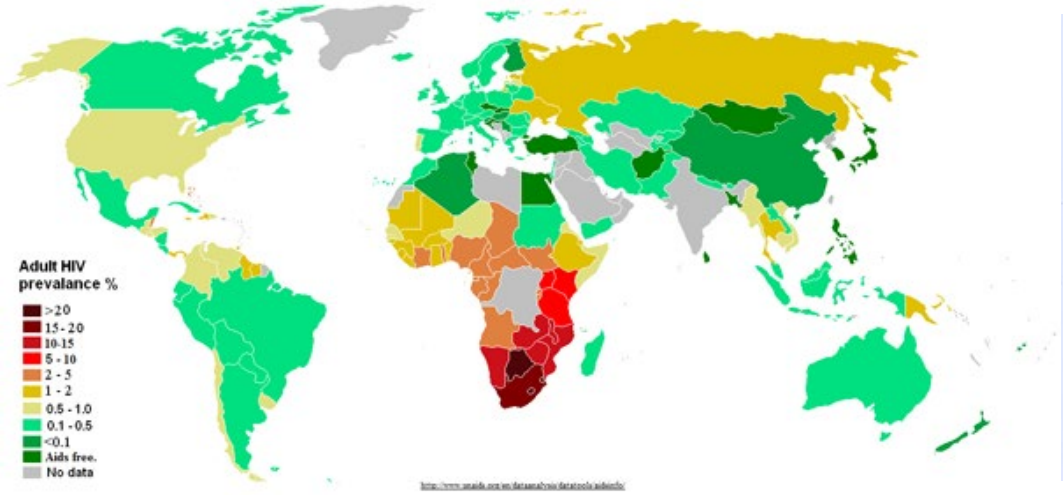
Omai Garner, PhD, D(ABMM)
Professor
Section Chief, Clinical Microbiology
Division Chief, Laboratory Medicine
Department of Pathology and Laboratory Medicine
UCLA Health

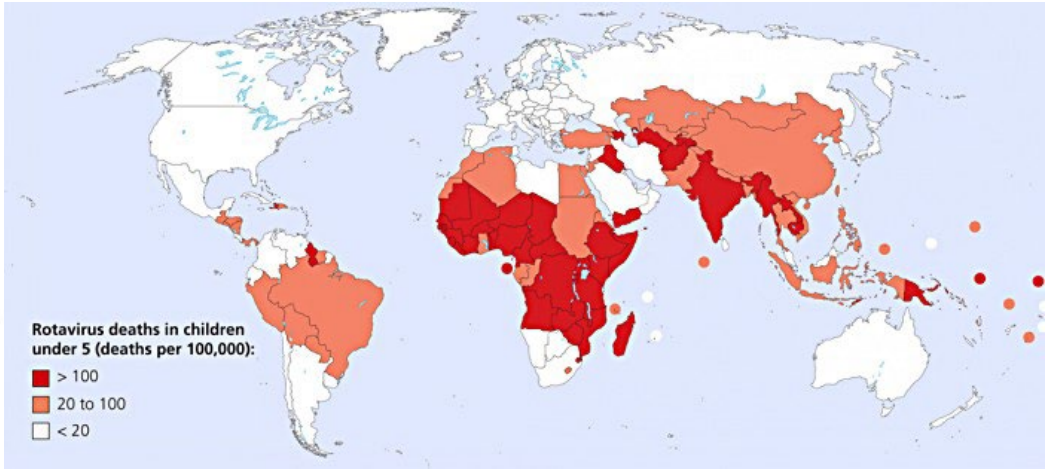
UCLA Health System

David Geffen School of Medicine

Unequal Global Burden of Infectious Disease

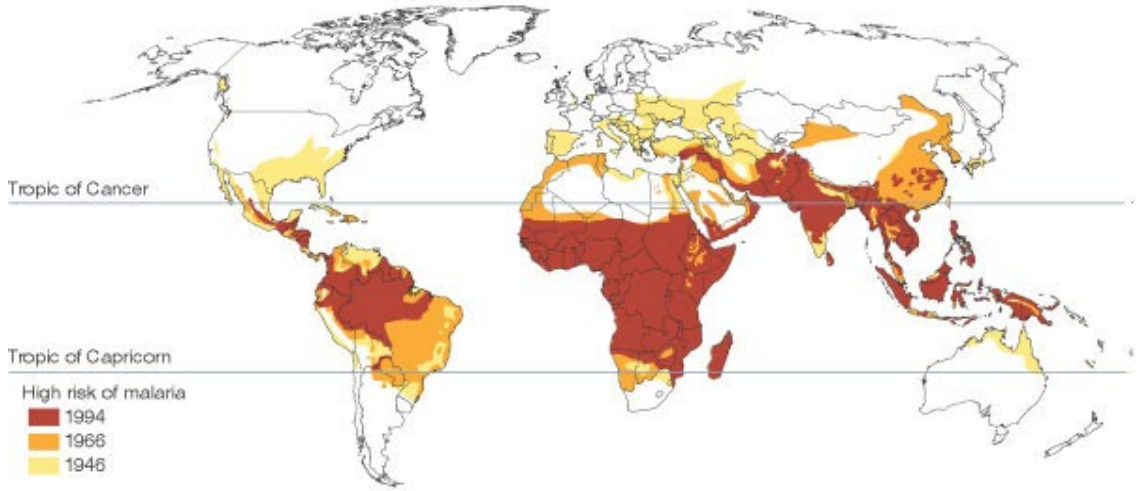
HIV

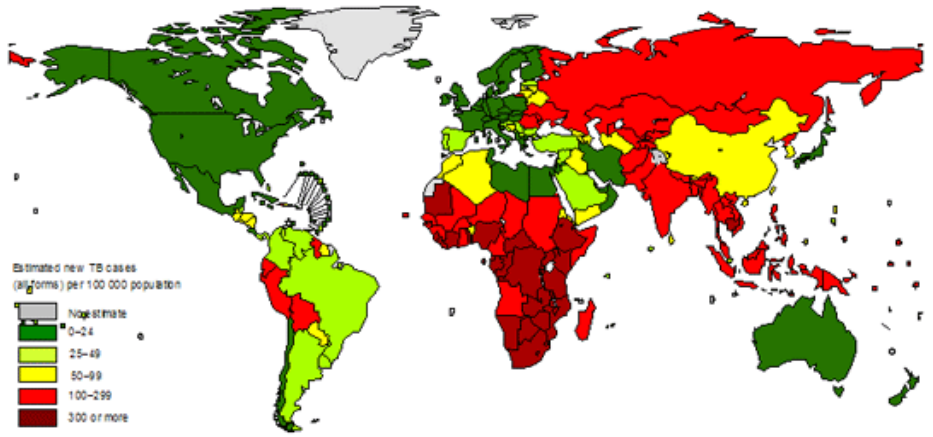




Diarrheal Disease (Rotavirus)

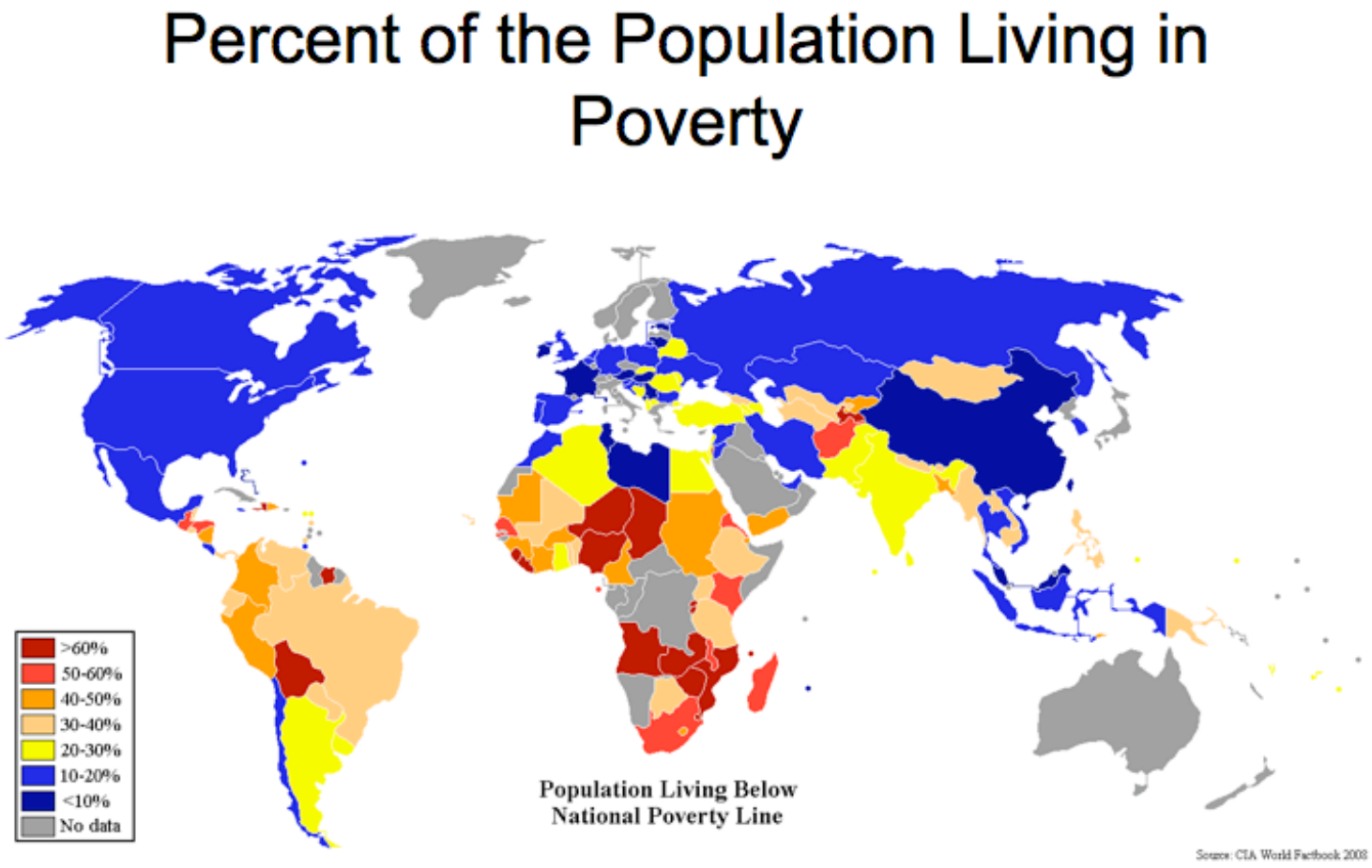
Malaria





TB

Infectious Disease Burden Correlates with Poverty



Resource limited countries account for 84% of the global population, and 90% of the global disease burden

Only account for 12% of global health expenditure

Yearly:
Acute respiratory infections -4.3 million deaths
Malaria – 500,000 deaths
AIDS and Tuberculosis – 5 million deaths

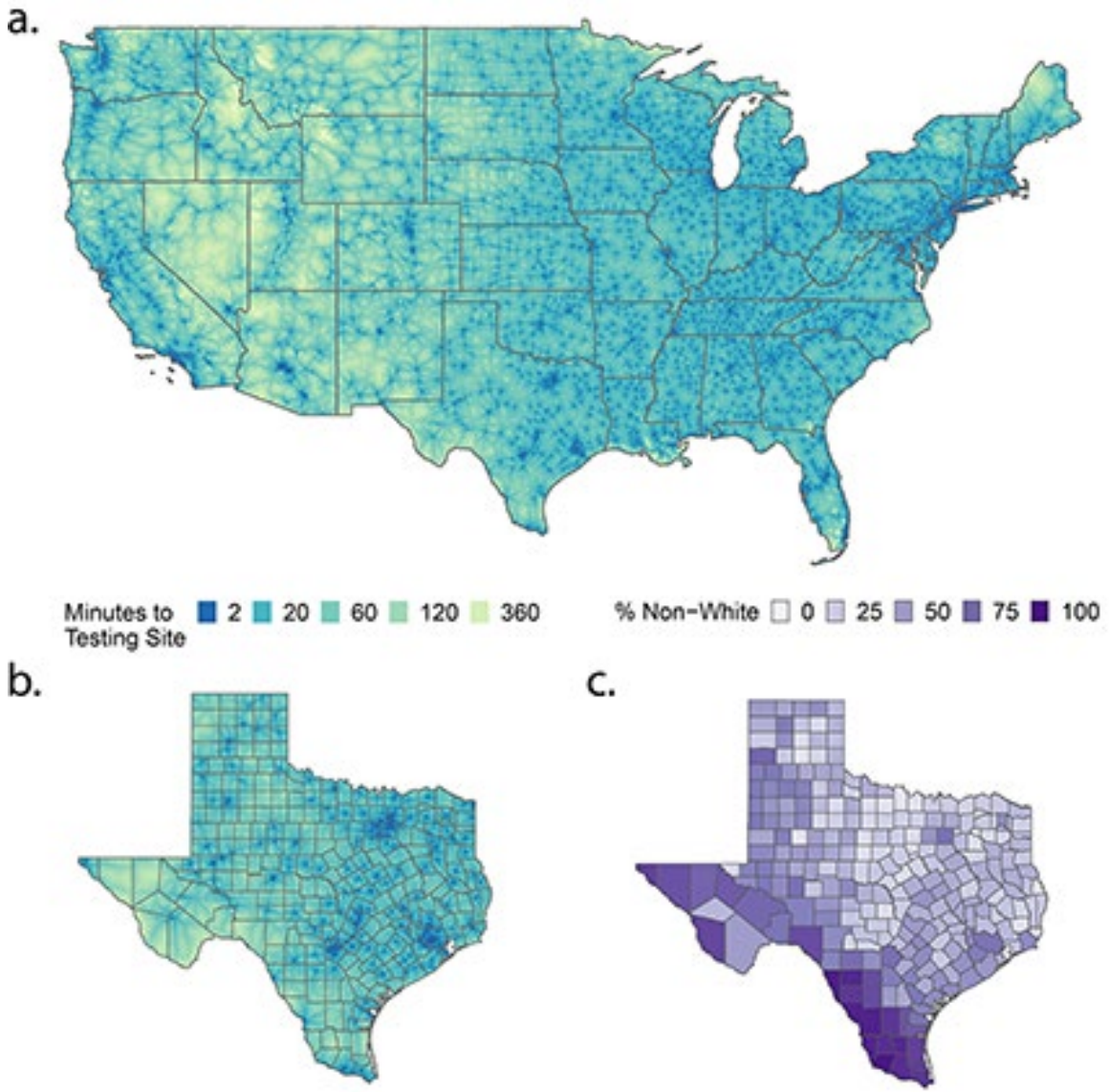
The Global Diagnostic Access Gap

47% of the global population has little to no access to diagnostics.

1.1 million premature deaths in low-income and middle-income countries could be avoided annually by reducing the diagnostic gap for six priority conditions:

- Diabetes
- Hypertension
- **HIV**
- **Tuberculosis** in the overall population
- **Hepatitis B virus** infection
- **Syphilis** for pregnant women

Equitable Access to Testing in the United States



April 2020 median travel time to a testing site was 20min

Percent minority was associated with an increase in travel time to a testing site

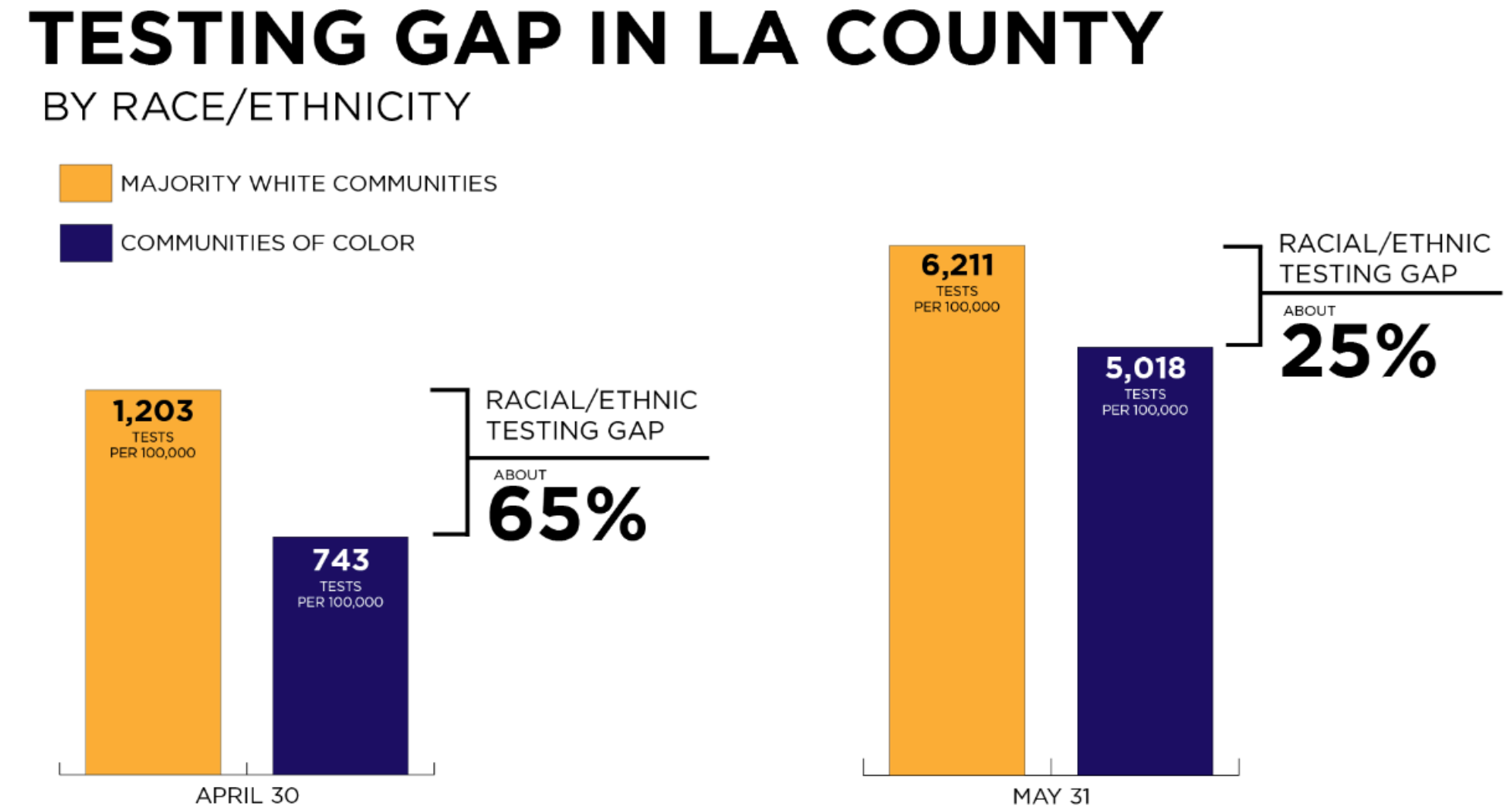
Percent uninsured associated with an increase in travel time to testing site

Rural plus uninsured → higher incidence of increased travel time to a testing site

Decreased access to testing sites in communities of color

Rader et al. J Travel Med (2020) 27(7)

COVID-19 Pandemic Revealed Existing Inequities in Lab Testing



Does the Clinical Laboratory Have a Role in Addressing Health Equity?

ACLS 2013 Position Paper:
Clinical laboratory services are the most cost effective, least invasive source of objective health information in disease prevention and diagnosis, improving patient outcomes, assuring patient safety, and fulfilling essential public health surveillance functions.

How do we bring clinical lab quality testing to patients that don’t have access to a clinical lab?

Working on Equitable Access to Lab Testing Exists Across a Spectrum

Novel Assay Component Development

New Antigen/Antibody targeted assays

New DNA/RNA targeted assays

Cheap, accessible readers

Clinical Test Development

Patient sample testing

Development and validation of clinical assays

Assay optimization for clinical care

Regulatory Approval

FDA preclinical and clinical trials

State licensure for testing

Clinical Test Implementation and Study

Launching novel tests for patient care

Studying clinical test effectiveness and impact

Clinical Diagnostic Access and Availability

Local and Global

Revealing Barriers

Expanding Services

Infrastructure and Training Support

History of Point of Care Testing

Ancient time- Tasting of urine for diabetes diagnosis

1960s-70s - Dipstick urinalysis, physician performed microscopy, fecal occult blood testing

Late 1980s – Handheld glucose meters intended for home use

Early 1990s – Handheld glucose meters used in the hospital to monitor patients

Issues arose related to accuracy, operator training, quality control and management of testing data in the medical record

Federal regulations expanded to cover point of care testing and physician office point of care came under scrutiny of regulatory organizations

CLIA: Clinical Laboratory Improvements Amendments

Federal regulations that control all clinical diagnostic testing

The Center for Medicare and Medicaid Services (CMS) regulates all diagnostic laboratory testing in the US through CLIA

The objective of CLIA is to ensure quality of all laboratory testing

CLIA ‘88 defined test complexity system

Waived Testing
(Doesn’t require a CLIA licensed laboratory or licensed test users)

Non-Waived Testing (Moderate to High Complexity)
(Requires a CLIA licensed laboratory and licensed test users)

What Point of Care Infectious Disease Tests Currently Exist ?

Parasitic Disease

African Trypanosomiasis
Trypanosomiasis
Plasmodium falciparum (Malaria)
Giardia
Cryptosporidium
Visceral Leishmaniasis
Schistosomiasis
Lymphatic filariasis

Bacterial/Mycobacterial Disease

Chlamydia
Group A Streptococcus
Syphilis
Tetanus
Tuberculosis
Legionnaire's disease
Streptococcus pneumoniae

Viral Disease

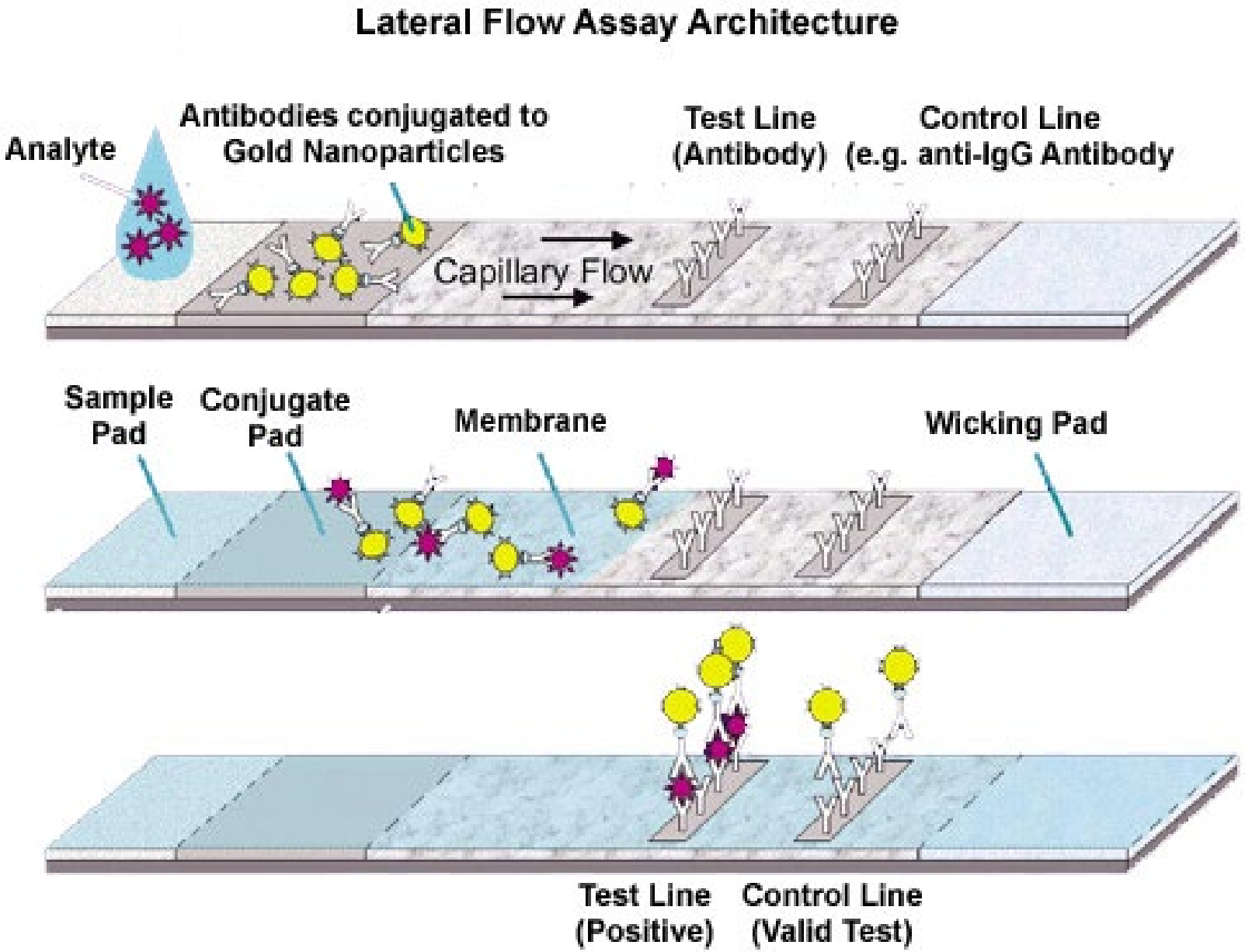
HIV
Hepatitis C
Influenza A and B
Respiratory Syncytial Virus (RSV)
Dengue
EBV

Fungal Disease

Cryptococcus

But this is a global list – far fewer are FDA approved and CLIA Waived

Point of Care Testing Methodology

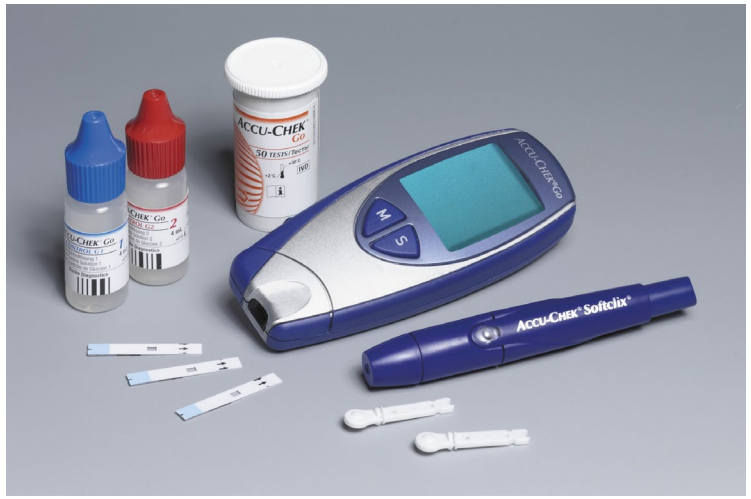


Point of Care Testing Errors

2000-2001 – Center for Medicare and Medicaid Services (CMS) undertook a national survey of labs/offices performing waived point of care tests

CMS directly observed 436 laboratories with certificates of waiver in 8 states

Tests consist of any of 56 tests granted “waived” status from CLIA



Point of Care Testing Errors

Sources of error –

Test operator incompetence –
19% of testing personnel had neither been trained or evaluated in performance of assays
32% could not locate test instructions when asked

Non-adherence to procedure –
25% failed to follow manufacturers instructions
7% did not perform required calibrations when necessary

Uncontrolled reagents and equipment –
32% failed to perform QC
6% used expired reagents and kits

COVID, Flu A/B, RSV POC Rapid Testing (Antigen Testing)

Abbott Binax Now
Manual result read

Quidel Sofia 2
Machine result read

BD Veritor
Machine result read

Advantages: Rapid result turn-around time (5-15 minutes)

Disadvantages: Lack of sensitivity. Only works well when the viral load is highest

EUA approved only for symptomatic illness and all of the package insert data (90% sensitivity compared to PCR) in the first 3-5 days of symptomatic illness

Rapid Testing (Antigen Testing)

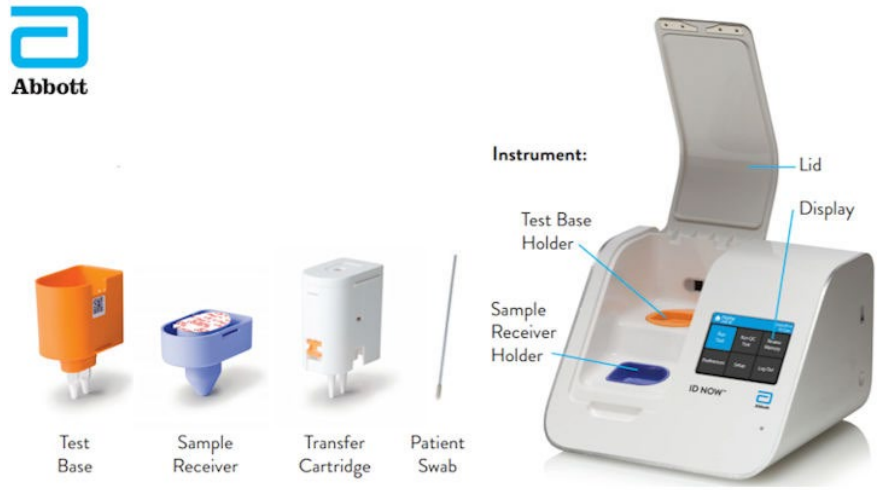
Antigen tests had an average sensitivity of 56% compared to RT-PCR and average specificity of 99.5%

(8 evaluations in 5 studies on 943 samples but not on any of the available tests in the US)

Unpublished data for Abbott Binax Now – Positive results up to a 30CT value compared to an RT-PCR test

Rapid, point-of-care **antigen** and molecular-based tests for diagnosis of SARS-CoV-2 infection.
Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, Hooft L, Leeflang MM, Spijker R, Van den Bruel A; Cochrane COVID-19 Diagnostic Test Accuracy Group.
Cochrane Database Syst Rev. 2020 Aug 26;8:CD013705. doi: 10.1002/14651858.CD013705.

COVID, Flu A/B, RSV POC Rapid Testing (Molecular but not RT-PCR)



Abbott ID Now

Isothermal amplification method:
Nicking enzyme amplification reaction (NEAR)

Advantages: Rapid resulting for a positive specimen (less than 15 minutes)

Disadvantages: Technique sacrifices sensitivity for speed

76.8% average sensitivity and 99.6% specificity as compared to RT-PCR (5 studies with 1003 samples total with 496 confirmed SARS CoV-2)

Rapid, point-of-care **antigen** and molecular-based tests for diagnosis of SARS-CoV-2 infection. Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, Hooft L, Leeflang MM, Spijker R, Van den Bruel A; Cochrane COVID-19 Diagnostic Test Accuracy Group. Cochrane Database Syst Rev. 2020 Aug 26;8:CD013705. doi: 10.1002/14651858.CD013705.

COVID, Flu A/B, RSV POC Rapid Testing (RT-PCR)

Cepheid Xpert Xpress

Roche Cobas Liat
FDA EUA approval on September 17, 2020

Advantage: RT-PCR results available in 30-45 minutes
Disadvantage: Low throughput and not available

99.4% sensitivity and 96.8% specificity compared to in-lab RT-PCR for the Xpert Xpress
6 studies with 919 samples, 479 confirmed SARS CoV-2

Rapid, point-of-care **antigen** and molecular-based tests for diagnosis of SARS-CoV-2 infection. Dinnes J, Deeks JJ, Adriano A, Berhane S, Davenport C, Dittrich S, Emperador D, Takwoingi Y, Cunningham J, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Taylor-Phillips S, Hooft L, Leeflang MM, Spijker R, Van den Bruel A; Cochrane COVID-19 Diagnostic Test Accuracy Group. Cochrane Database Syst Rev. 2020 Aug 26;8:CD013705. doi: 10.1002/14651858.CD013705.

Summary of Near Patient Testing Landscape (US)

Very few tests are FDA approved and CLIA waived for Infectious Disease

Point of Care Antigen based tests are inexpensive but suffer from lack of multiplexing, lack of sensitivity, and can be subjective in result interpretation.
$500 Antigen readers, $10-$20 a test

Point of Care Molecular tests that are not PCR can have reduced cost compared to PCR but also have a lack of comparative sensitivity and lack multiplexing
$4,000 molecular instruments, $30-$40 a test

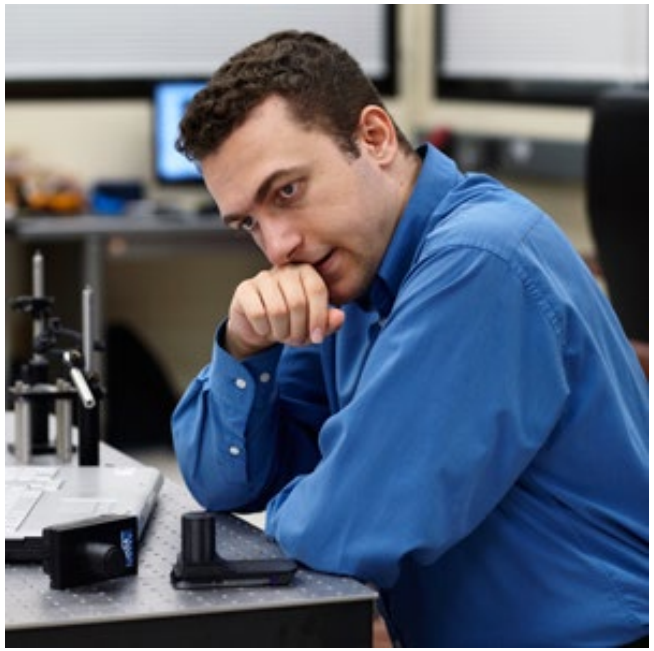
Point of Care PCR based molecular tests are very sensitive, but lack multiplexing and are very expensive
$12,000 PCR machines, $50-$60 a test

The Need:
An inexpensive, multiplexed, sensitive near patient testing system

UCLA Cross-Disciplinary Research Team - POC Diagnostics

Dino Di Carlo, PhD
Professor
Department of BioEngineering
UCLA

Microfluidics



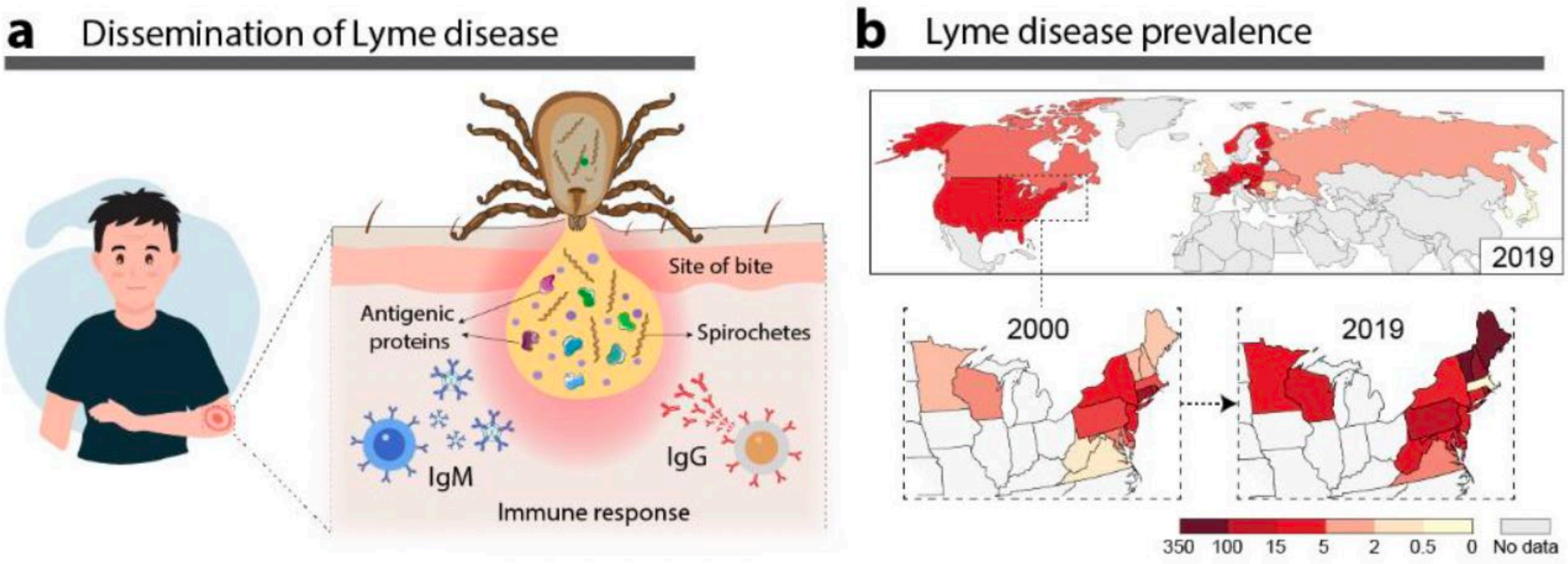
Aydogan Ozcan, PhD
Chancellor's Professor
HHMI Professor
Department of Electrical Engineering
UCLA

Imaging and Sensing Architecture

Development of a Novel Point-of-Care Lyme Diagnostics

Goal: Achievement of simple, low-cost, rapid and multiplexed detection of Lyme specific IgMs and IgGs

Challenge: Multiplexing (2 out of 3 IgMs and 5 out of 10 IgGs) while maintaining sensitivity/specificity

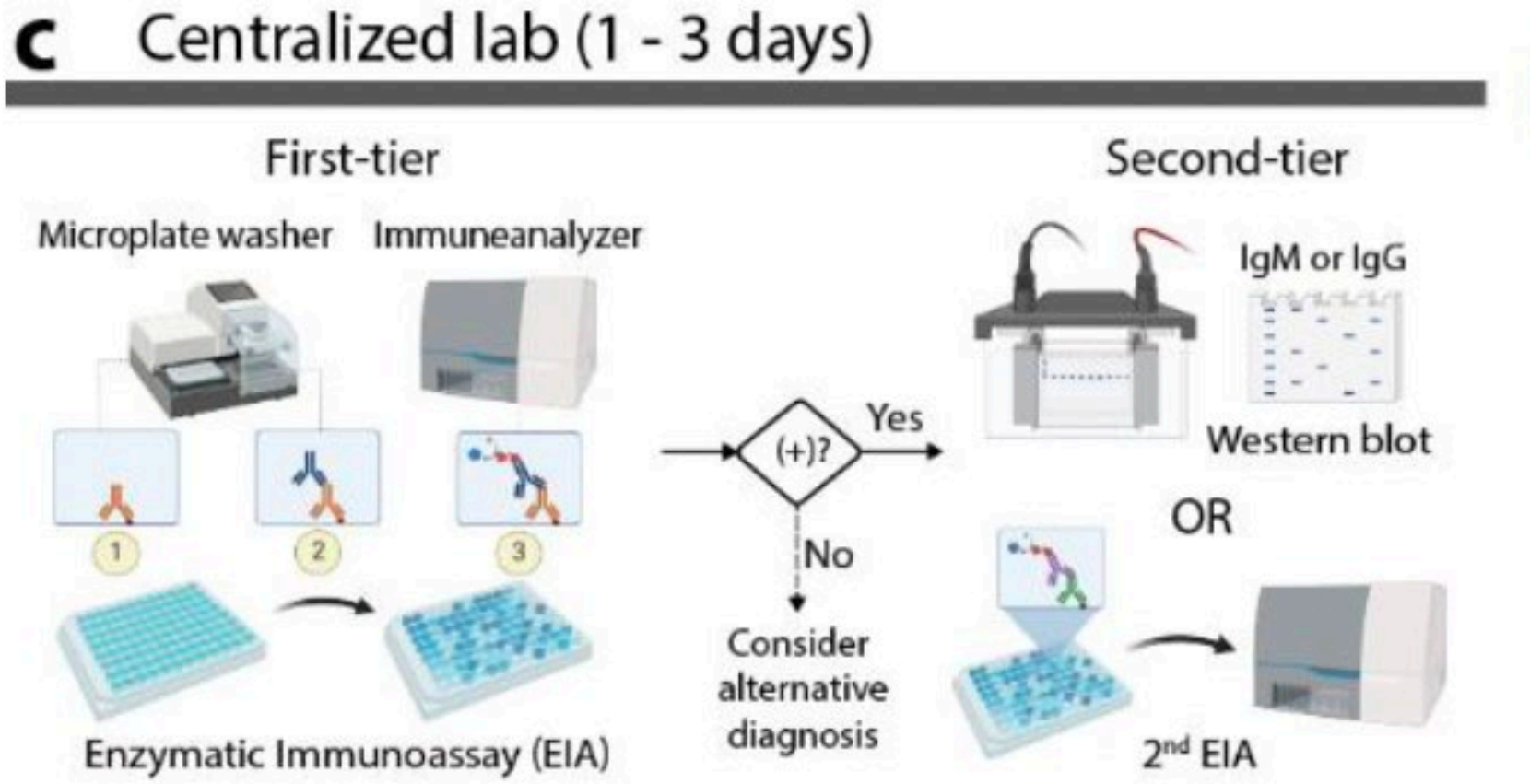


Create a platform that is flexible – able to incorporate novel relevant antigens and antibodies for better specificity and sensitivity for rapid and multiplexed Lyme detection

Development of a Novel Point-of-Care Lyme Diagnostics

Goal: Achievement of simple, low-cost, rapid and multiplexed detection of Lyme specific IgMs and IgGs

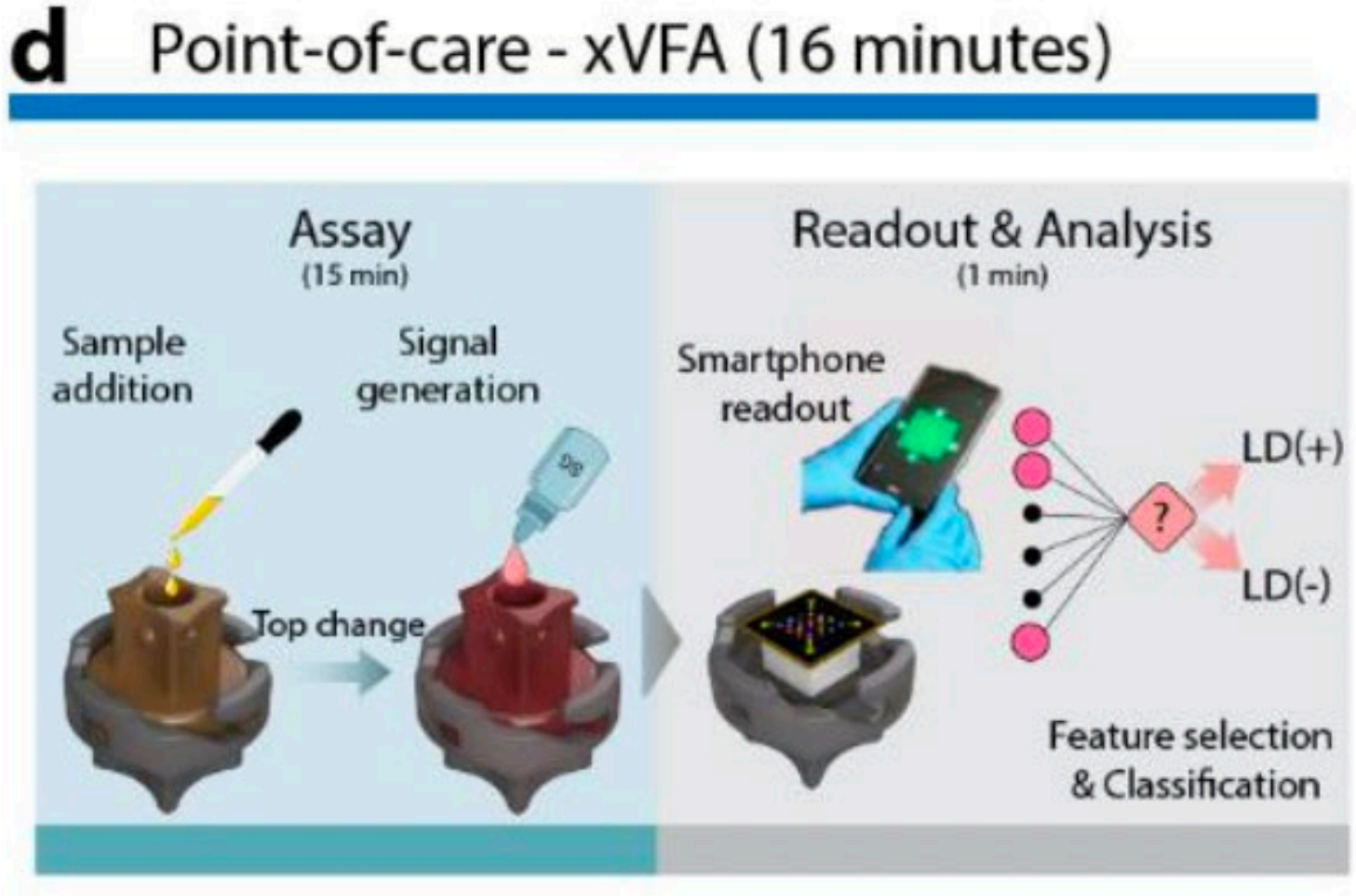
Challenge: Multiplexing (2 out of 3 IgMs and 5 out of 10 IgGs) while maintaining sensitivity/specificity



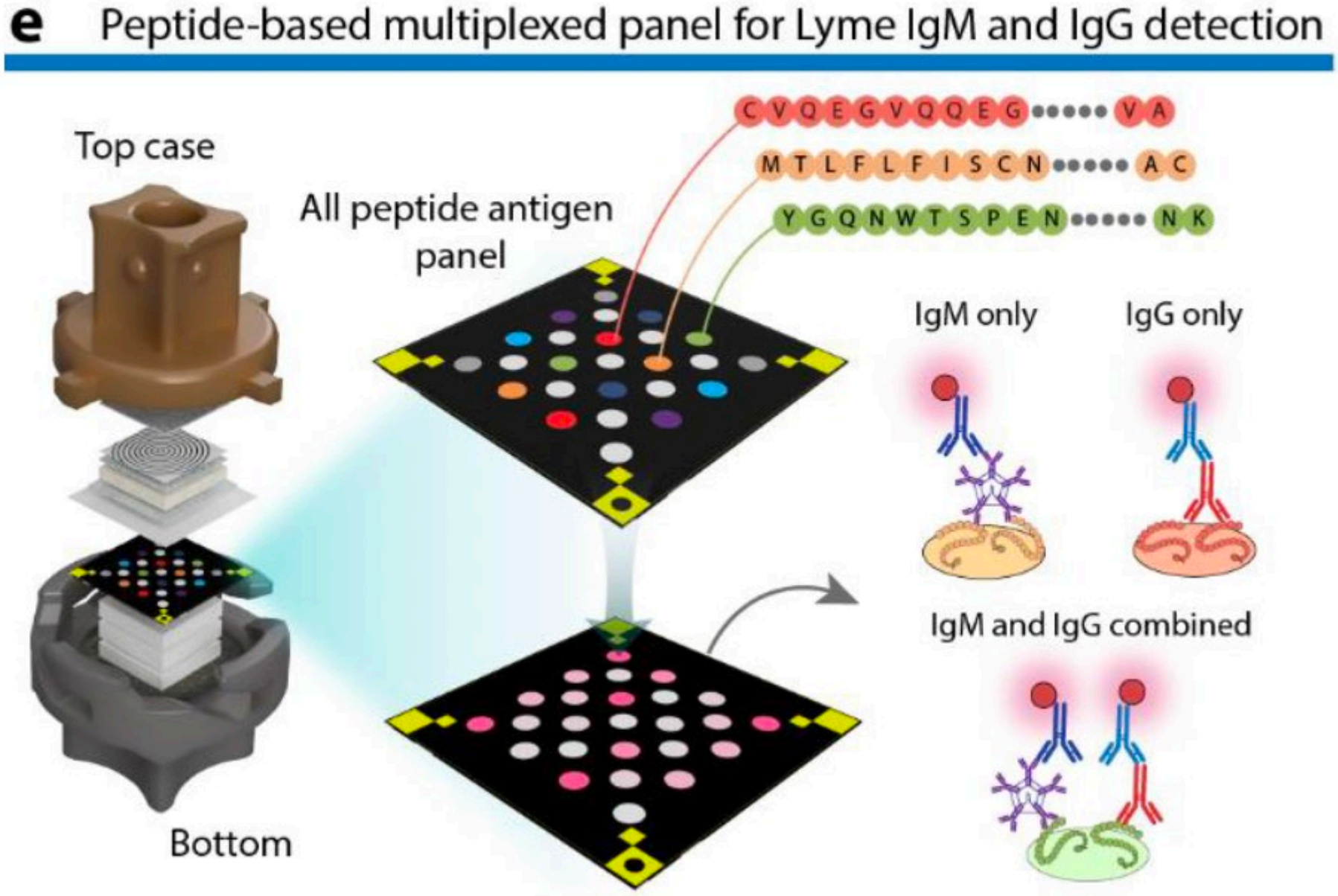
Development of a Novel Point-of-Care Lyme Diagnostics

Goal: Achievement of simple, low-cost, rapid and multiplexed detection of Lyme specific IgMs and IgGs

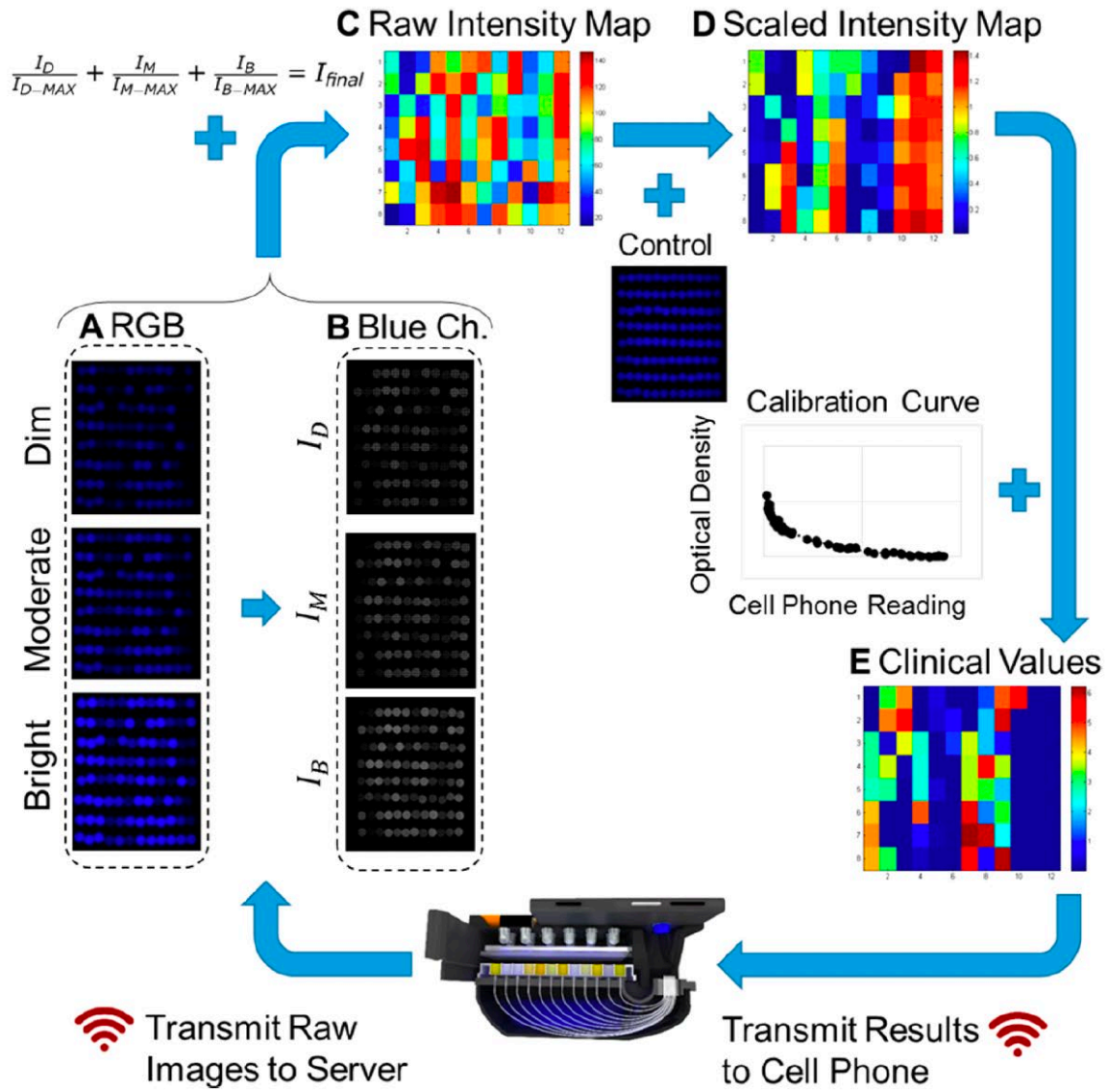
Challenge: Multiplexing (2 out of 3 IgMs and 5 out of 10 IgGs) while maintaining sensitivity/specificity

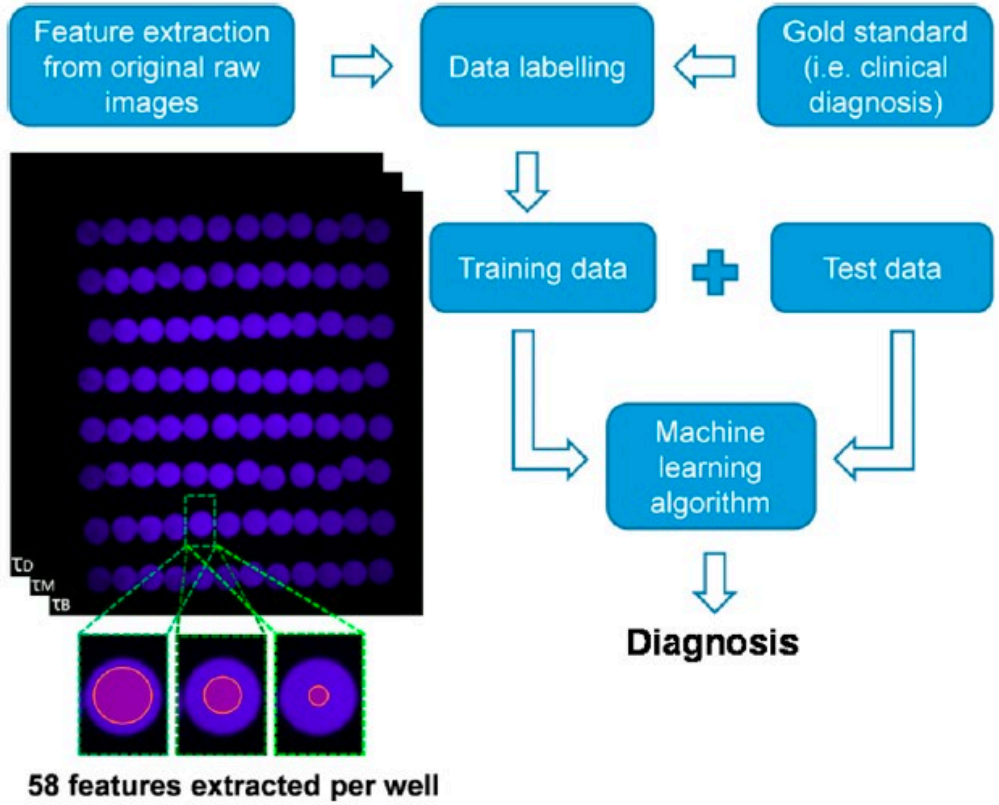


Development of a Novel Point-of-Care Lyme Diagnostics

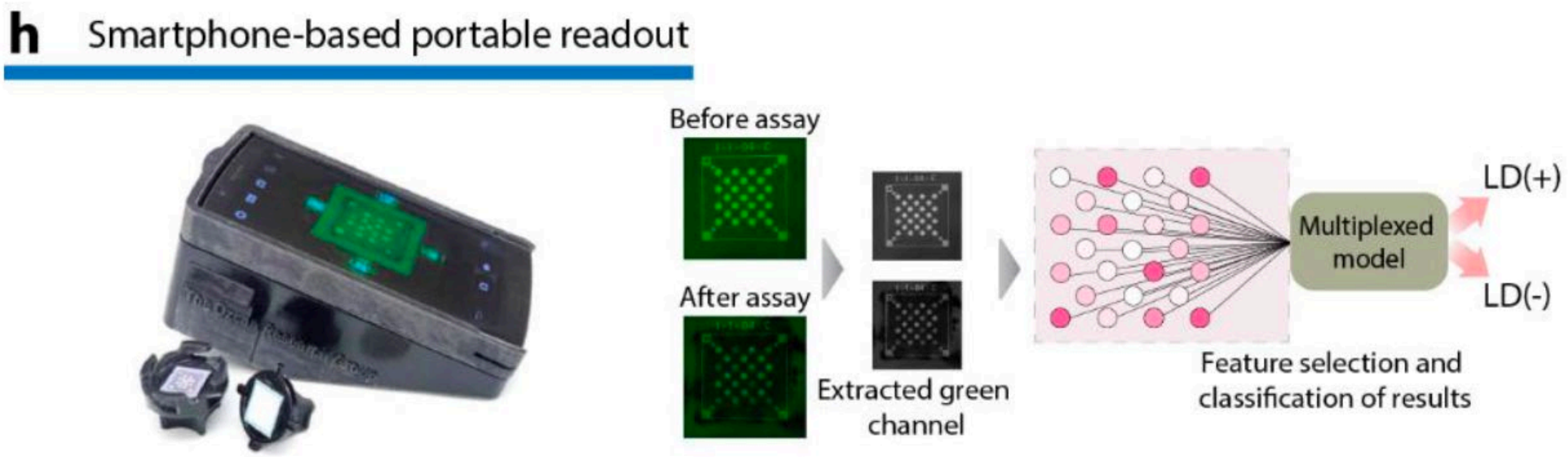


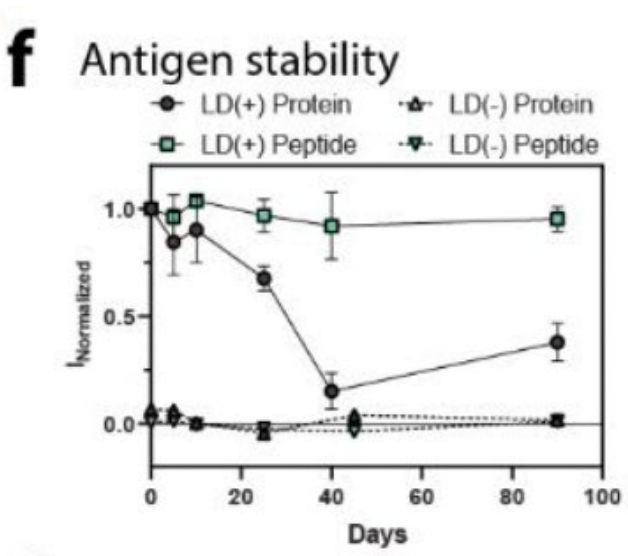
Everything Good in Engineering Requires Machine Learning (AI)

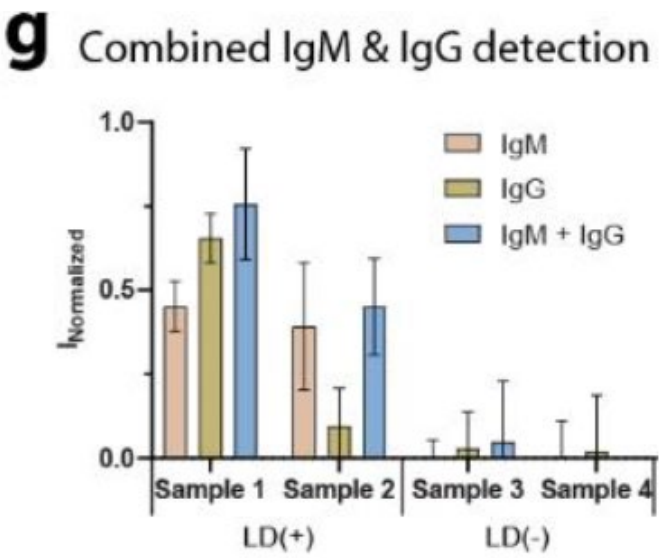




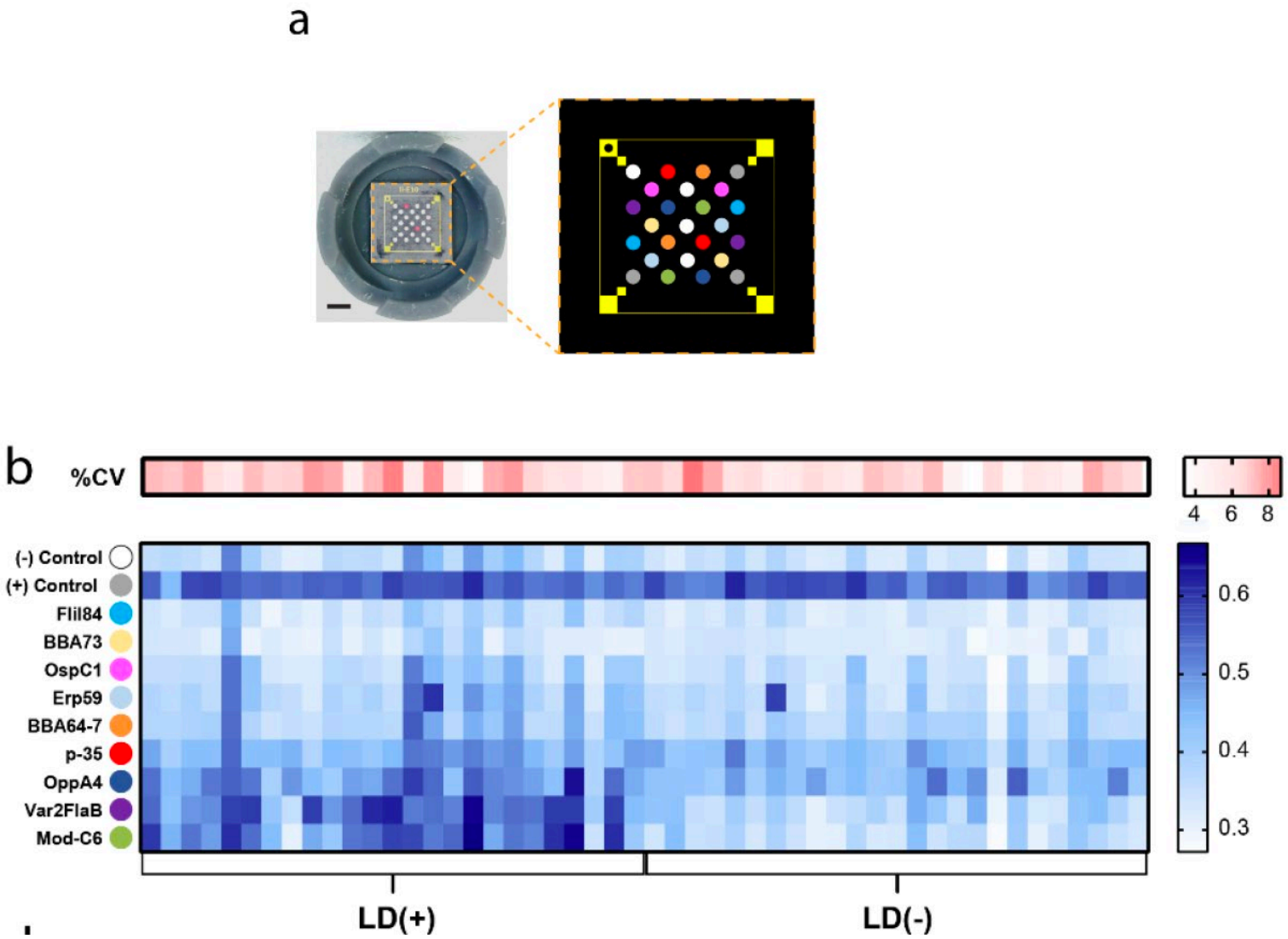
Development of a Novel Point-of-Care Lyme Diagnostics

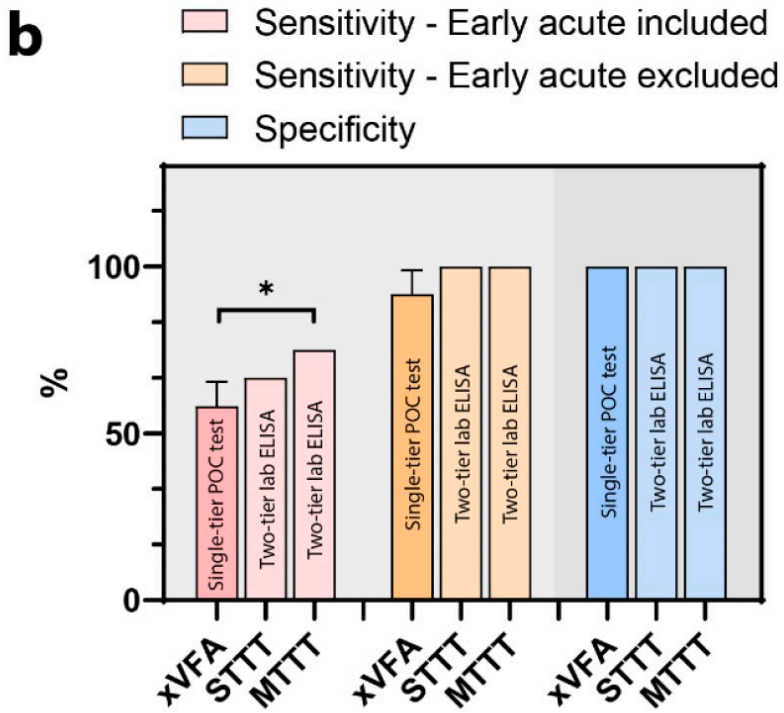




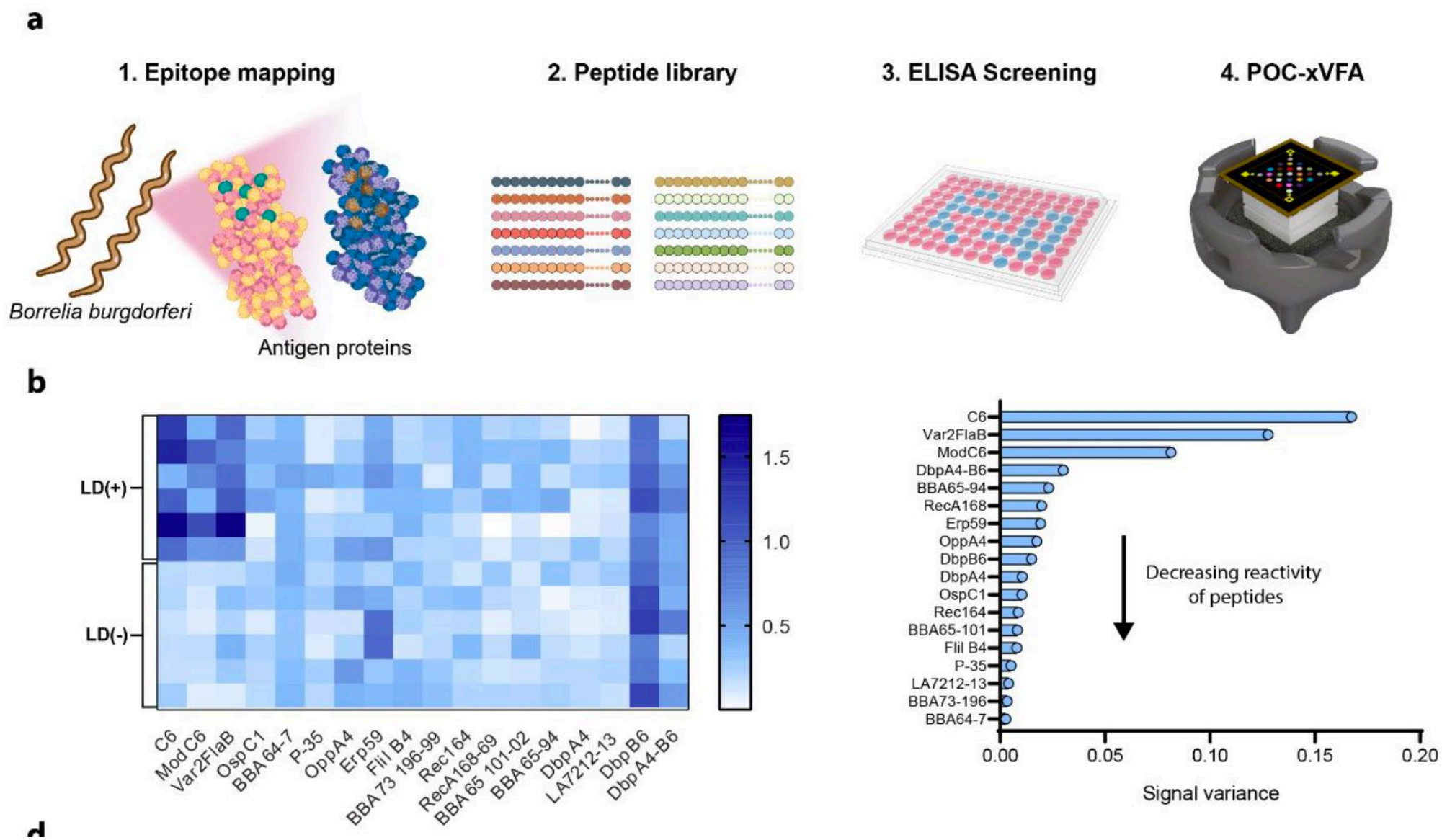


Novel Clinical Test Performs Well Compared to Two-Tiered Assay





Can Quickly Test New Targeted Peptides for Effectiveness



Decreased Cost and Potential for Increased Availability

Supplementary Table 5. Cost breakdown of xVFA test using recombinant proteins and peptide-based antigen panel.

Types	Name	Cost/test ($)	
		Antigen assay	Peptide assay
Paper materials	Asymmetric membrane	0.38	
	Interpad	0.07	
	NC membrane	0.17	
	Catridge (3D printed)	1.00	
Bio/chemical resources	Gold nanoparticles	0.20	
	Anti-Human IgG	0.17	
	Anti-Human IgM	0.17	
	Anti-Mouse IgG	0.002	
	BSA	0.03	
	Others	0.40	
	Antigens	**10.4**	
	Peptides		**0.32**
	Total cost per test	**12.99**	**2.59**

UCLA Cross-Disciplinary Research Team - POC Diagnostics

Sam Emaminejad, PhD
Associate Professor
Department of Electrical Engineering
UCLA

Harold Monbouquette, PhD
Professor
Department of Chemical/
Biomolecular Engineering
UCLA

› Nature. 2022 Nov;611(7936):570-577. doi: 10.1038/s41586-022-05408-3. Epub 2022 Nov 9.

Ferrobotic swarms enable accessible and adaptable automated viral testing

Haisong Lin [# 1], Wenzhuo Yu [# 1], Kiarash A Sabet [# 1], Michael Bogumil [2], Yichao Zhao [1], Jacob Hambalek [2], Shuyu Lin [1], Sukantha Chandrasekaran [3], Omai Garner [3], Dino Di Carlo [4], Sam Emaminejad [5 6]

Affiliations + expand

PMID: 36352231 PMCID: PMC9645323 DOI: 10.1038/s41586-022-05408-3

› Sens Diagn. 2022 Nov 11;2(1):163-167. doi: 10.1039/d2sd00128d. eCollection 2023 Jan 19.

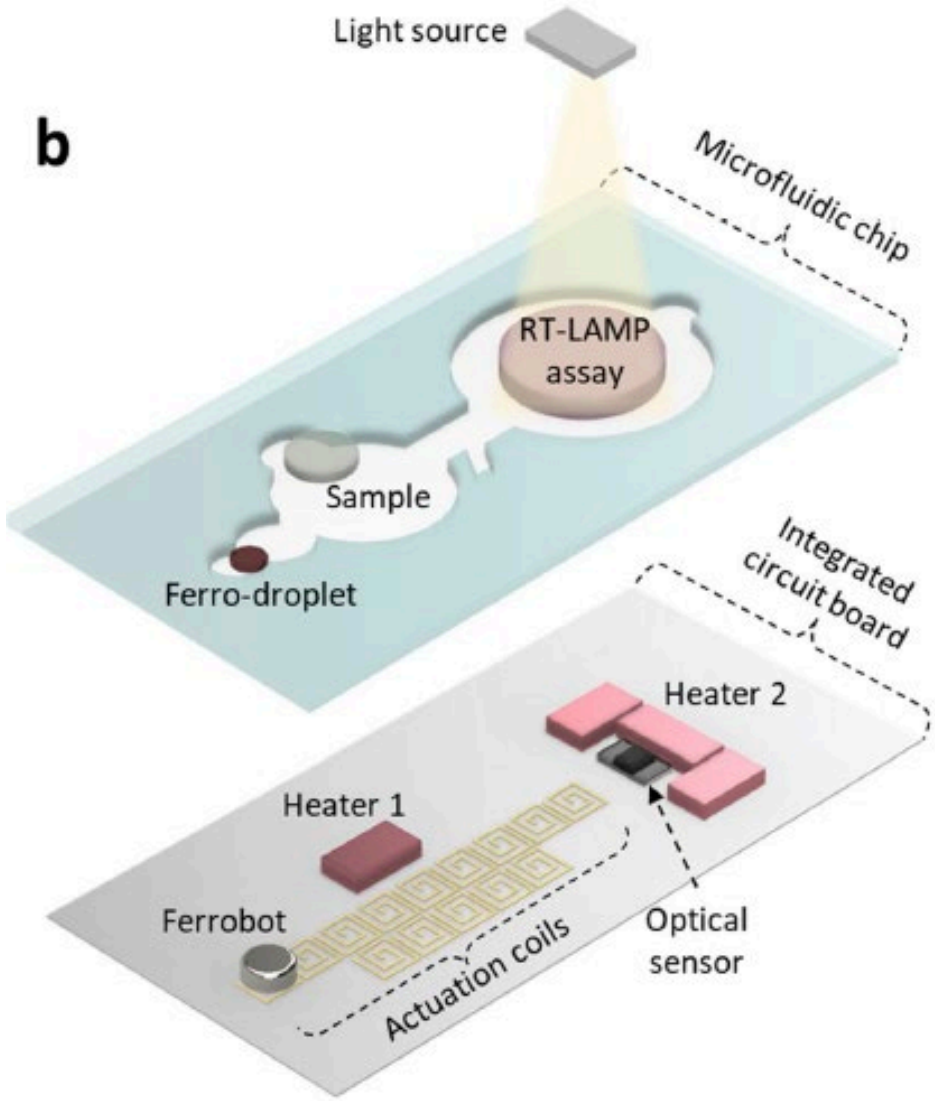
An amplification-free, 16S rRNA test for *Neisseria gonorrhoeae* in urine

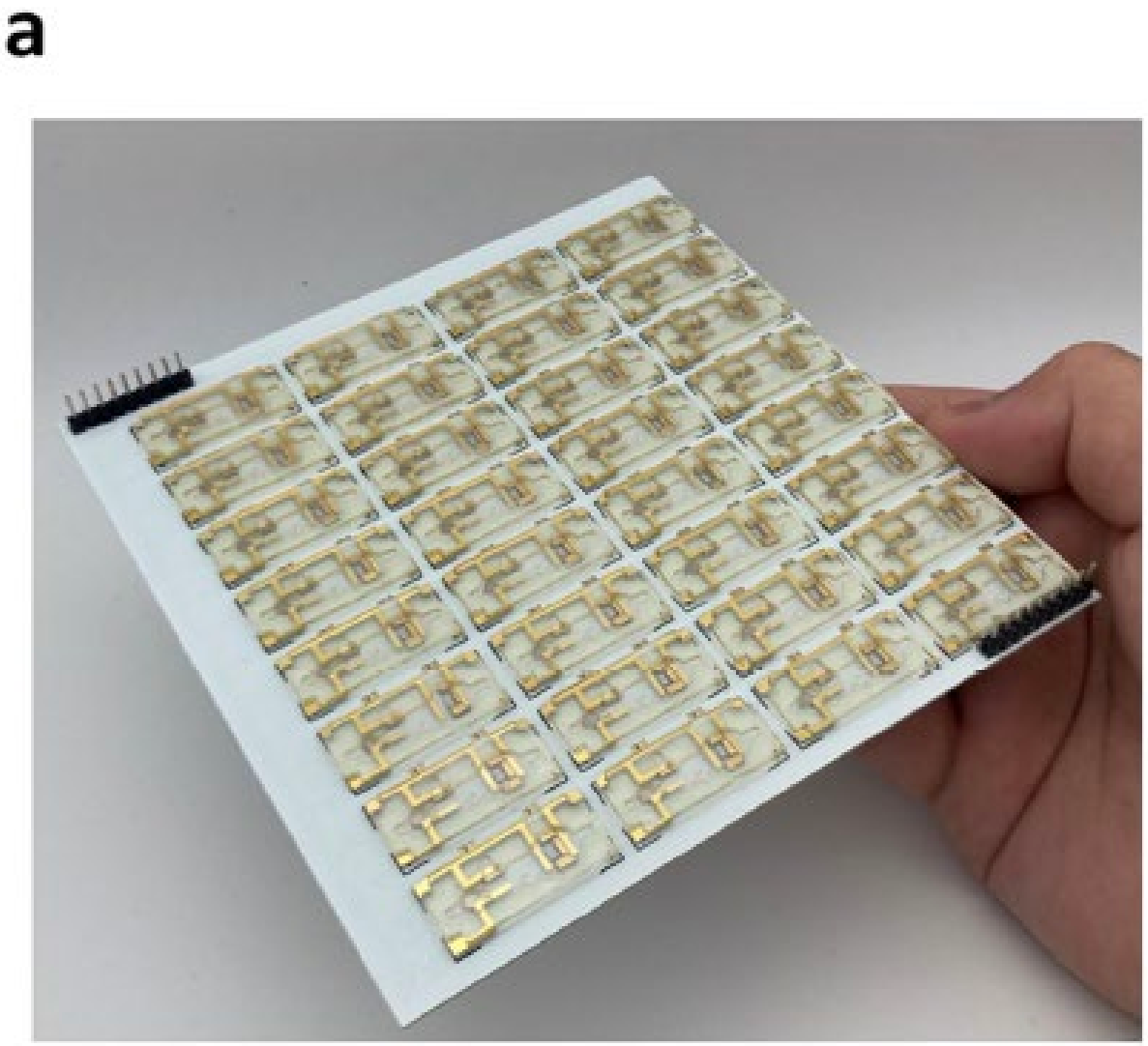
Zhenrong Zheng [1], Yan Cao [1], Sukantha Chandrasekaran [2], Jacob J Schmidt [3], Omai B Garner [2], Harold G Monbouquette [1]

Affiliations + expand

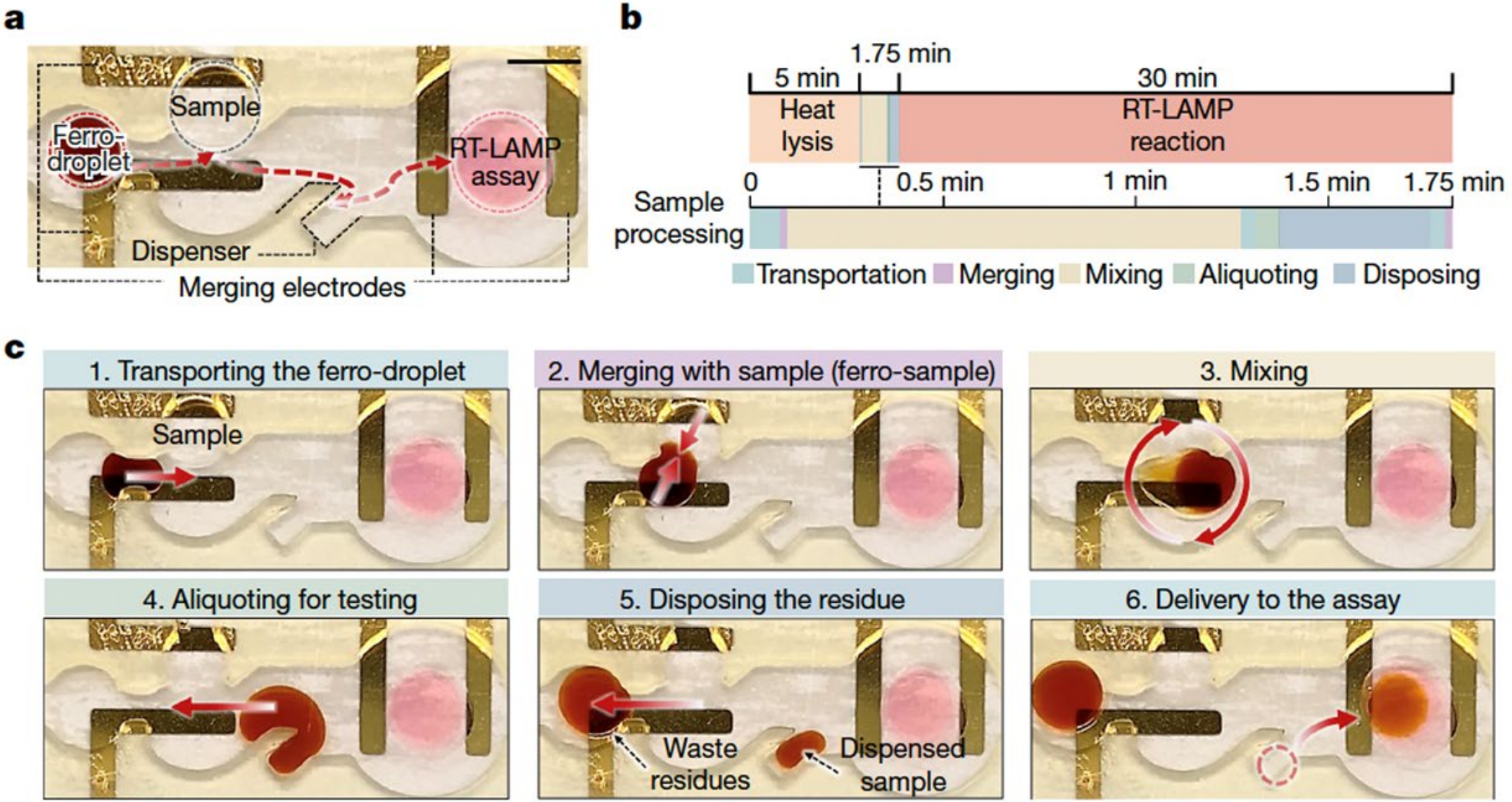
PMID: 36741249 PMCID: PMC9850355 DOI: 10.1039/d2sd00128d

Ferrobotic Swarms Enable Accessible and Adaptable Automated Viral Testing

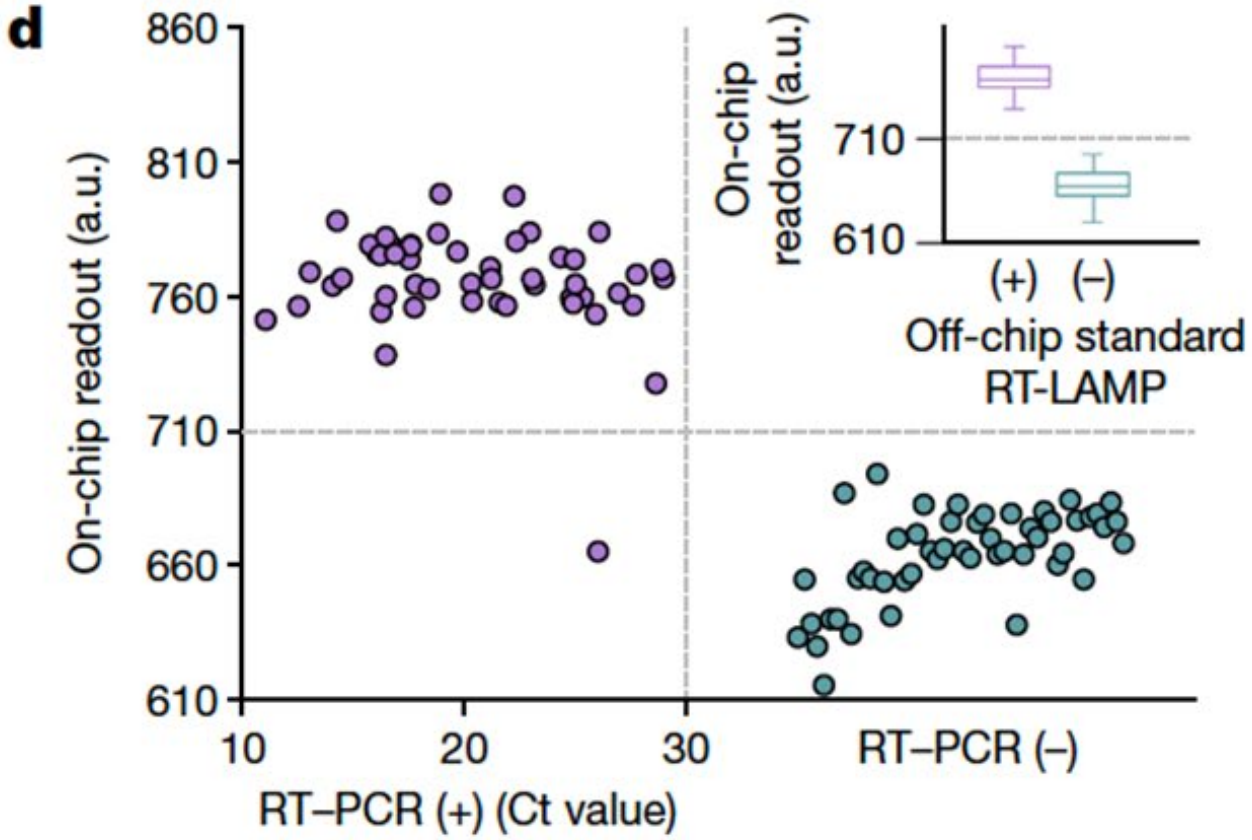


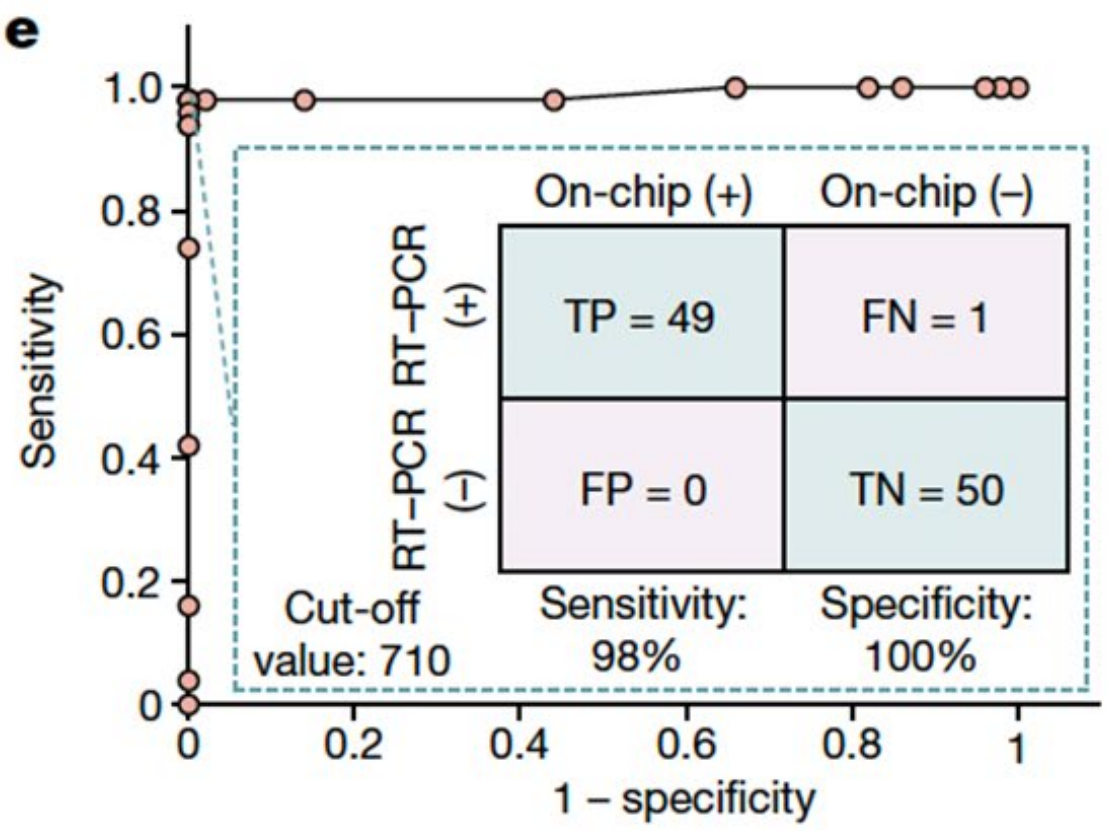


Ferrobotic Swarms Enable Accessible and Adaptable Automated Viral Testing

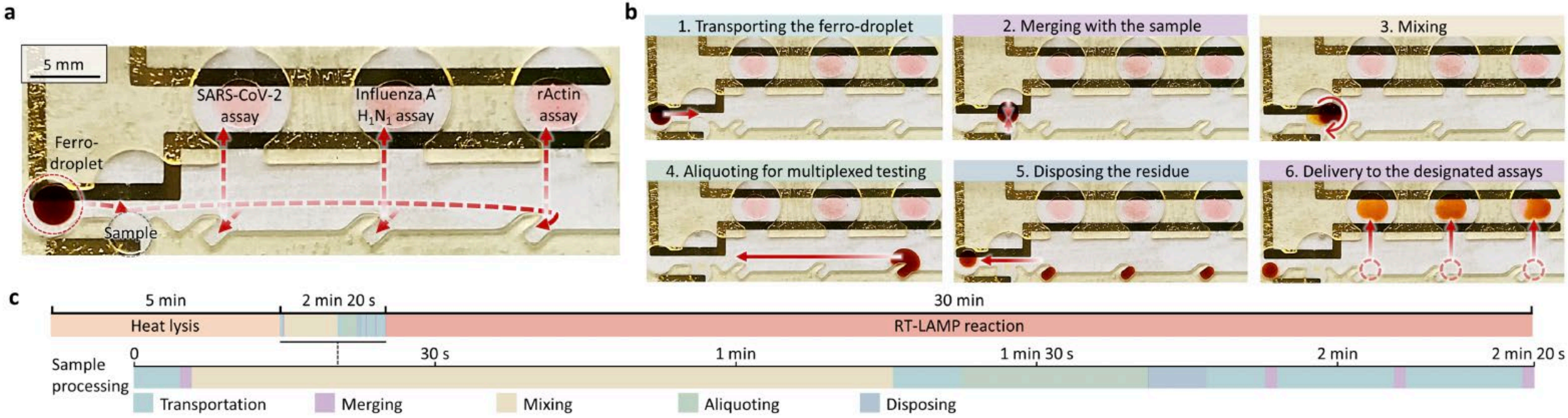


Ferrobotic Swarms Enable Accessible and Adaptable Automated Viral Testing

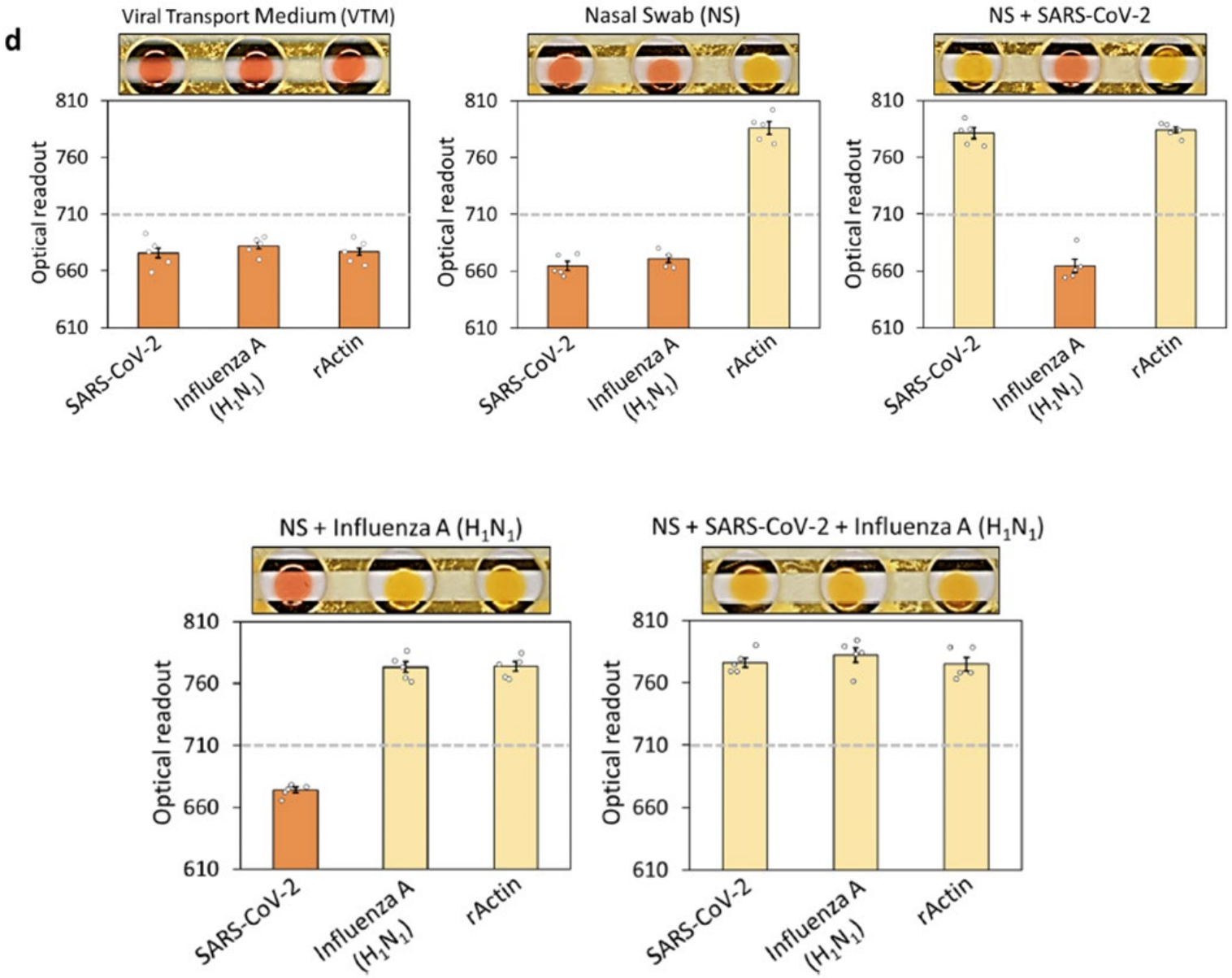




Ferrorobotic Swarms Enable Accessible and Adaptable Automated Viral Testing



Ferrorobotic Swarms Enable Accessible and Adaptable Automated Viral Testing



Working on Equitable Access to Lab Testing Exists Across a Spectrum

Novel Assay Component Development

New Antigen/Antibody targeted assays

New DNA/RNA targeted assays

Cheap, accessible readers

Clinical Test Development

Patient sample testing

Development and validation of clinical assays

Assay optimization for clinical care

Regulatory Approval

FDA preclinical and clinical trials

State licensure for testing

Clinical Test Implementation and Study

Launching novel tests for patient care

Studying clinical test effectiveness and impact

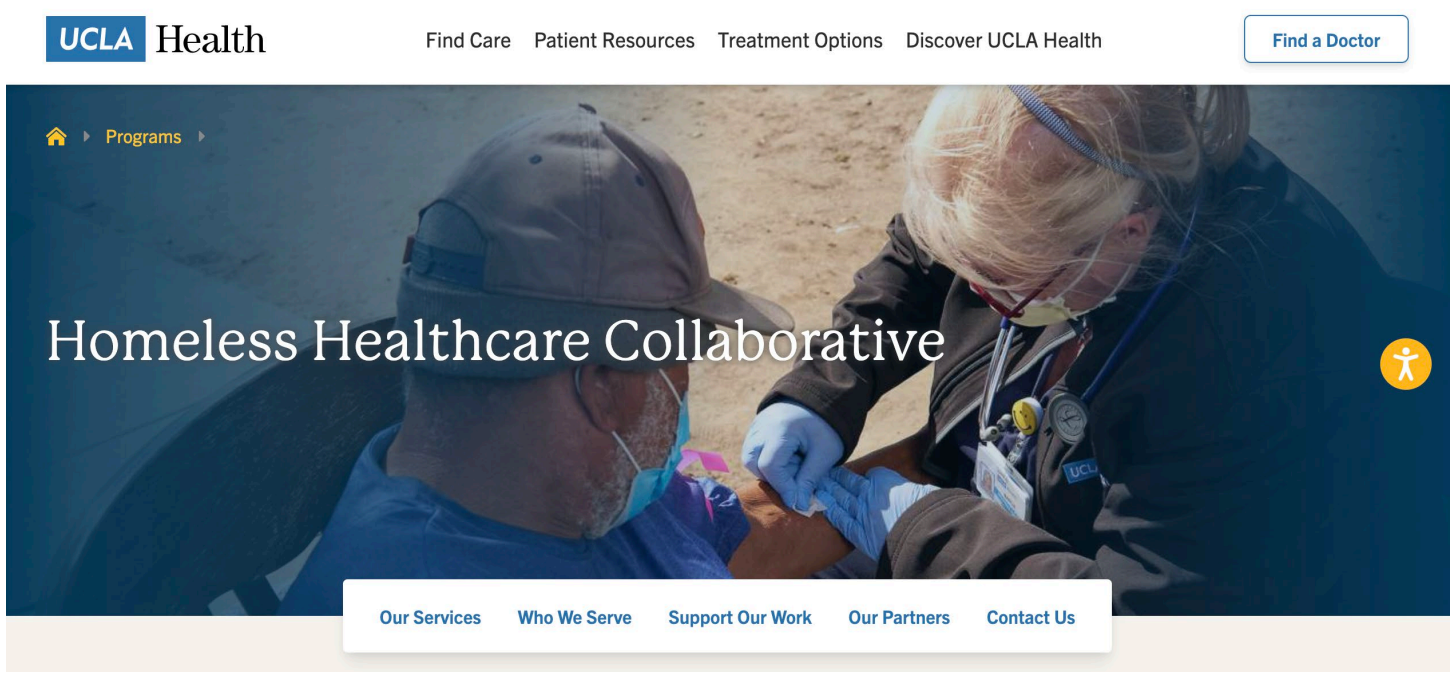
Clinical Diagnostic Access and Availability

Local and Global

Revealing Barriers

Expanding Services

Infrastructure and Training Support



In 2023, approx. 71,000 people experienced homelessness in Los Angeles County

American Indian/Alaskan Native, and Black Angelenos are 3x/4x more likely to experience homelessness

LatinX are the fastest growing group of people experiencing homelessness in LA County

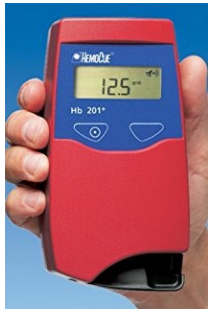
6 HHC vans provide medical services at shelters and encampments around Los Angeles

HHC had 5600 unique patient encounters, mean age 49 yrs old, 66% male, 33% female, 4 patients non-binary gender

Encounter Diagnosis	N	%
Essential hypertension	778	14
Musculoskeletal pain, not low back pain	425	8
Skin and subcutaneous tissue infections	347	6
Exposure, encounters, screening or contact with infectious disease	293	5
Nervous system pain and pain syndromes	271	5
Diabetes mellitus, Type 2	260	5
Fungal infections	191	3
Low back pain	189	3
Respiratory signs and symptoms	184	3

Ambulatory Care Sensitive Conditions	N	% of ACSCs
Anemia	14	0.8
Angina	20	1.2
Asthma	112	6.6
Cellulitis	347	20.3
Congestive heart failure	25	1.5
Chronic obstructive pulmonary disease	84	4.9
Dental Condition	107	6.3
Diabetes	277	16.2
Epilepsy	36	2.1
Gangrene	4	0.2
Gastroenteritis	4	0.2
Hypertension	795	46.6
Pneumonia	12	0.7
Urinary tract infection	31	1.8
Ulcer	49	2.9

Point of Care Testing in a Van



- CLIA Certificate of Waiver in a mobile lab
- Training of MD and nursing staff and competencies
- CareConnect (EPIC) access on the van for result recording
- QC logs
- Instrument Maintenance in a Van setting

Infectious Disease Testing for HHC

Current State:

RSV Antigen, Influenza A antigen, Influenza B Antigen, COVID Antigen, Group A Strep

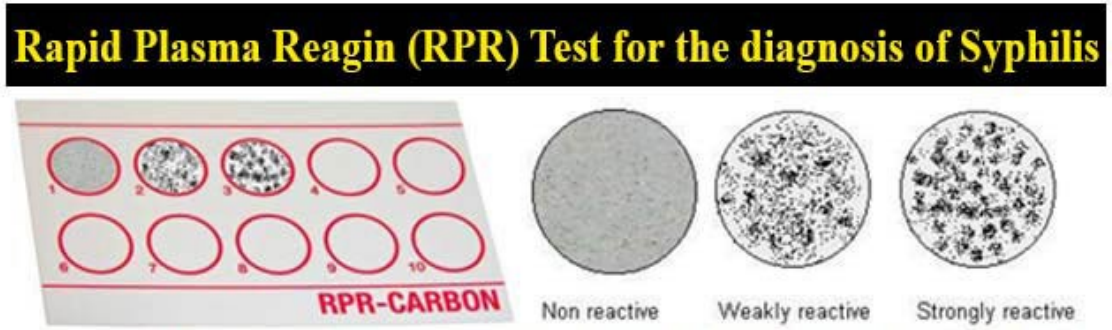
Quidel Sofia (Lateral Flow with a Reader)

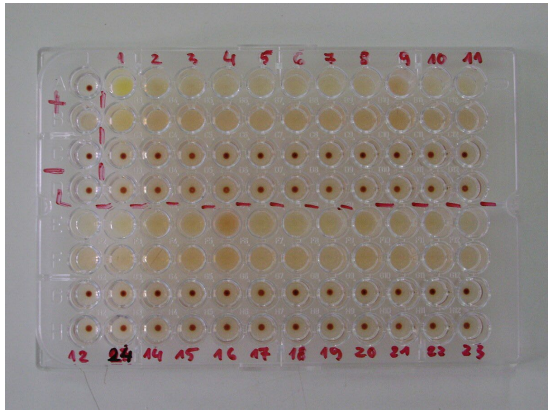
Future State:

HIV 4th Gen (Lateral Flow, Manual Read)
Syphilis Antibody (Lateral Flow, Manual Read)

CLIA Waived PCR Testing: Gonorrhea/Chlamydia . . .

Rapid Syphilis Testing





Conventional Syphilis testing: RPR plus TPPA
Reverse algorithm Syphilis testing: Syphilis Antibody plus RPR
Average TAT for a positive: 24-48 hours

Rapid Syphilis Antibody Testing: Lateral flow for T. pallidum specific antibodies
Average TAT: 20 min

Positive for Antibody: Secondary, latent, tertiary, and treated syphilis

Rapid 4th Gen HIV Testing

Fingerstick whole blood
TAT 20 minutes

2 lines that registers either p24 antigen or HIV antibodies

Requires follow up testing on a positive signal

Negative test results do not exclude early infection
Questionable sensitivity for lower HIV viral load positive patients

Rapid CT/GC PCR Testing

January 21, 2025: Roche Cobas Liat gets FDA approval and CLIA Waiver for STI

PCR test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*

20 minute TAT to results

Approved on Vaginal Swabs and Male Urine (Female urine, rectal, and pharyngeal testing will be submitted to the FDA in the future)

Rapid HCV PCR Testing

Cepheid Xpert Xpress has CLIA Waiver for fingerstick PCR HCV RNA testing

45 to 60 minute TAT to results

Positive results for genotypes 1-6

Limit of Detection is 35-160 IU/mL HCV viral RNA (depending on genotype)

In-Field Near-Patient Chlamydia and Gonorrhea Testing for Patients Experiencing Housing Insecurity

Background:

- High rates of STI exposure among people experiencing homelessness
- Undiagnosed and untreated Chlamydia and gonorrhea increase risk of HIV acquisition
- People experiencing homelessness face barriers to receiving both preventive and acute care, limiting opportunities for them to be screened for STIs and be eligible for preventive services such as DoxyPEP and PrEP.

Study Objectives:

- Implement point-of-care (POC) PCR testing for chlamydia and gonorrhea (CT/GC) using the Roche Cobas Liat for direct-in-community healthcare for unhoused persons
- Compare empiric and targeted antibiotic prescription rates for individuals presenting with a chief concern related to STIs before and after implementation of the Roche Cobas Liat CT/GC POC test
- Assess feasibility of using CT/GC POC test in routine screening for STI for sexually active women as recommended by US Preventive Services Task Force
- Assess feasibility of using CT/GC POC test in initiation and routine screening for STIs for patients on DoxyPEP, per CDC guidelines
- Assess feasibility of using CT/GC POC test in initiation and routine screening for STIs for patients on Pre-exposure Prophylaxis for HIV, per CDC guidelines

Many points of entry to contribute to Lab Access and Equity
Choose what excites you the most!

Novel Assay Component Development

New Antigen/Antibody targeted assays

New DNA/RNA targeted assays

Cheap, accessible readers

Clinical Test Development

Patient sample testing

Development and validation of clinical assays

Assay optimization for clinical care

Regulatory Approval

FDA preclinical and clinical trials

State licensure for testing

Clinical Test Implementation and Study

Launching novel tests for patient care

Studying clinical test effectiveness and impact

Clinical Diagnostic Access and Availability

Local and Global

Revealing Barriers

Expanding Services

Infrastructure and Training Support

Acknowledgements

PATHS-UP

UCLA Clinical Microbiology Lab

UCLA Point of Care Team

Society of Black Lab Directors