Innovation in Point-of-Care Testing Technologies and Access

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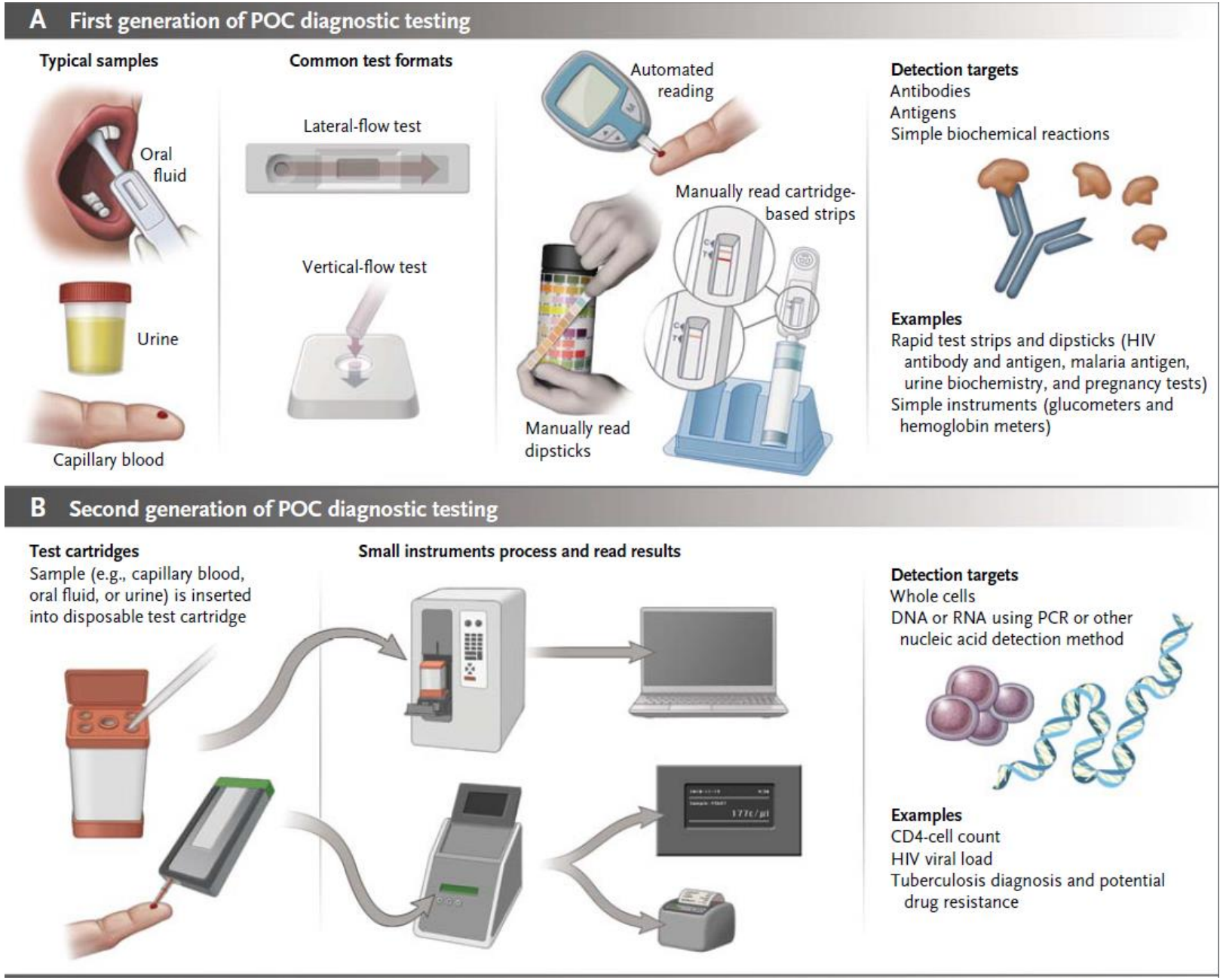
1st Australasian Conference on POC Testing for Infectious Diseases

March 14, 2023

Center for Innovative Diagnostics for Infectious Diseases



Jani IV & Peter T NEJM 2013

- Influenza A & B, *Trichomonas vaginalis*[2], bacterial vaginitis, hepatitis B, trypanosomiasis
- Limited to low CD4 (HIV) - *Cryptococcus neoformans*, tuberculosis (TB) LAM[3]
- Need confirmatory test – syphilis[4], hepatitis C, HIV[5]
- Proof-of-concept *Neisseria gonorrhoeae*[6]

- Sample-to-answer: chlamydia & gonorrhea, TB, SARS-CoV-2, influenza A & B, RSV, HIV, global fever panel (18 multiplex)[7]
- Plasma only - HIV viral load

1.FDA EUA; 2. Osom – Huppert JS J Clin Microbiol 2005; 3. Wake RM CID 2023; 4. Marks M Exp Rev Mol Diag 2017; 5. Ma S Exp Rev Mol Diag 2023; 6. Peters R IUSTI 2022; 7. Manabe YC Lancet ID 2022;

Diversification of Molecular Platforms

	Company	Platform	Targets	Sample types	TAT (min)
	**Cepheid (USA)**	Xpert	TB, HIV, SARS-CoV-2, influenza A &B, RSV, NG/CT, enterovirus, Mpox, strep A, TV, GBS, C.diff, norovirus, AMR, biomarkers	Whole blood, plasma, nasal swab, vaginal swab, urine, stool, CSF	42-92 min
	**Diagnostics for the Real World (UK)**	SAMBA II	HIV, SARS-CoV-2, influenza, RSV		90 min
	**Abbott (USA)**	m-PIMA	HIV (M, N, O subtypes)	Plasma	52 min
	**Molbio (India)**	TrueNat	HIV, tuberculosis, SARS-CoV-2, malaria, dengue, chikungunya, influenza A & B, salmonella, HBC, rabies, CT/NG, TV, HPV, GBS, hepatitis (A, E), Nipah, Scrub T, cholera	Whole blood, plasma, nasal swab, vaginal swab, urine, stool, CSF	40+ min extraction time (20 min)

HIV Self-Tests: WHO Pre-Qualified

Test (Manufacturer)	Specimen	Generation	Approval
OraQuick® In-Home HIV Test (OraSure Technologies, USA)	Oral	2nd, HIV 1/2 antibodies	FDA / WHO PQ
OraQuick® HIV Self-Test (OraSure Technologies, USA)	Oral	2nd, HIV 1/2 antibodies	WHO PQ
INSTI™ HIV Self Test (BioLytical Laboratories Inc., Canada)	Blood	2nd, HIV 1/2 antibodies	WHO PQ
SURE CHECK® HIV Self-Test (Chembio Diagnostic Systems, Inc, USA)	Blood	2nd, HIV 1/2 antibodies	WHO PQ
Mylan HIV Self-Test (Atomo Diagnostics Pvty. Ltd, Australia)	Blood	3rd, HIV 1/2 antibodies	WHO PQ
Check Now™ HIV Self Test (Abbott Rapid Diagnostics, Germany)	Blood	3rd, HIV 1/2 antibodies	WHO PQ

Limited Menu of FDA Cleared STI Assays in US

Point-of care

Binx NG/CT

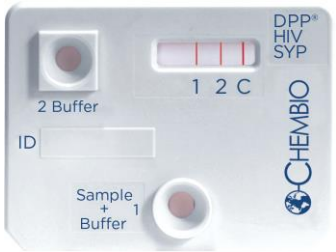
Visby NG/CT/TV

Osom TV

Trinity syphilis

Solana TV*

Cepheid NG/CT*



Chembio HIV/syphilis

Over-the-counter (OTC) Self-Test

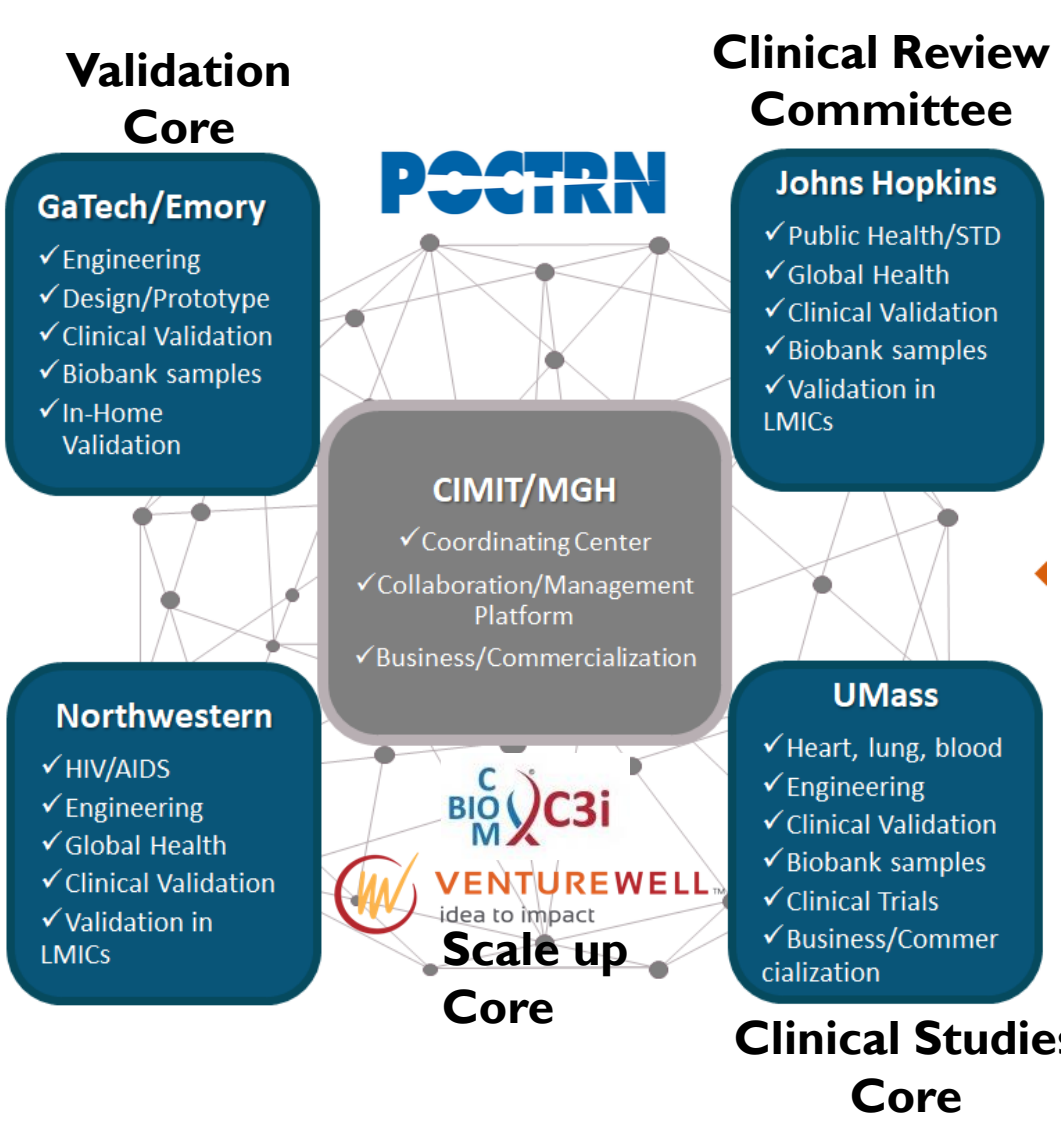
*CLIA-waiver (use at POC by a paraprofessional without training) not yet granted

Manabe YC Clin Chem 2021

Generation 3

…molecular detection…faster, smaller, and battery operated

COVID-19 Diagnostic Development: RADx Tech



NIH
National Institute of Biomedical Imaging and Bioengineering


Bruce Tromberg


Tiffani Lash


Todd Merchak

UNITED STATES CONGRESS

Lamar Alexander, Roy Blunt

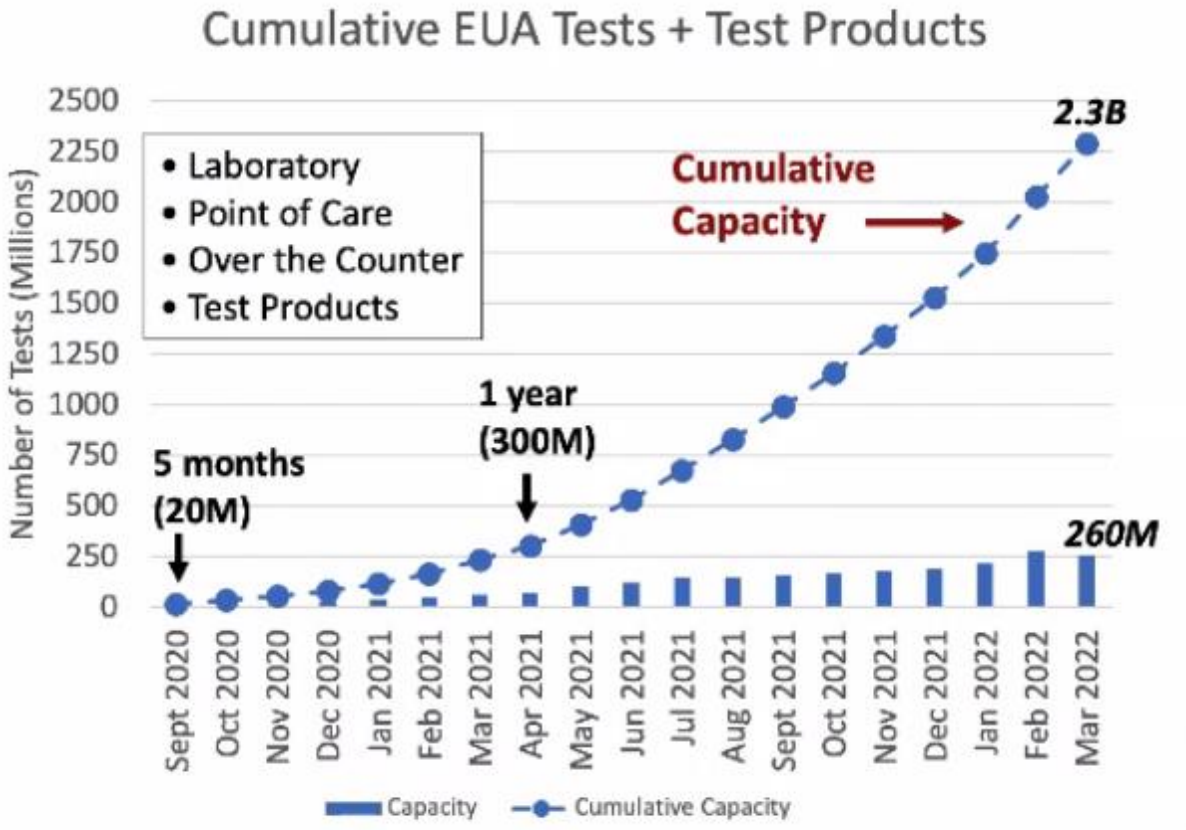
RADx Tech
RADx Advanced Technology Platforms
=~$1+ billion

CDC Centers for Disease Control and Prevention
FDA
CMS Centers for Medicare & Medicaid Services

https://www.poctrn.org

Posted on April 20, 2020
https://www.washingtonpost.com/opinions/2020/04/20/how-speed-up-testing-shark-tank-government/

RADx Tech Impact: OTC Tests & Paradigm Shift



https://www.nibib.nih.gov/covid-19/radx-tech-program/radx-tech-dashboard

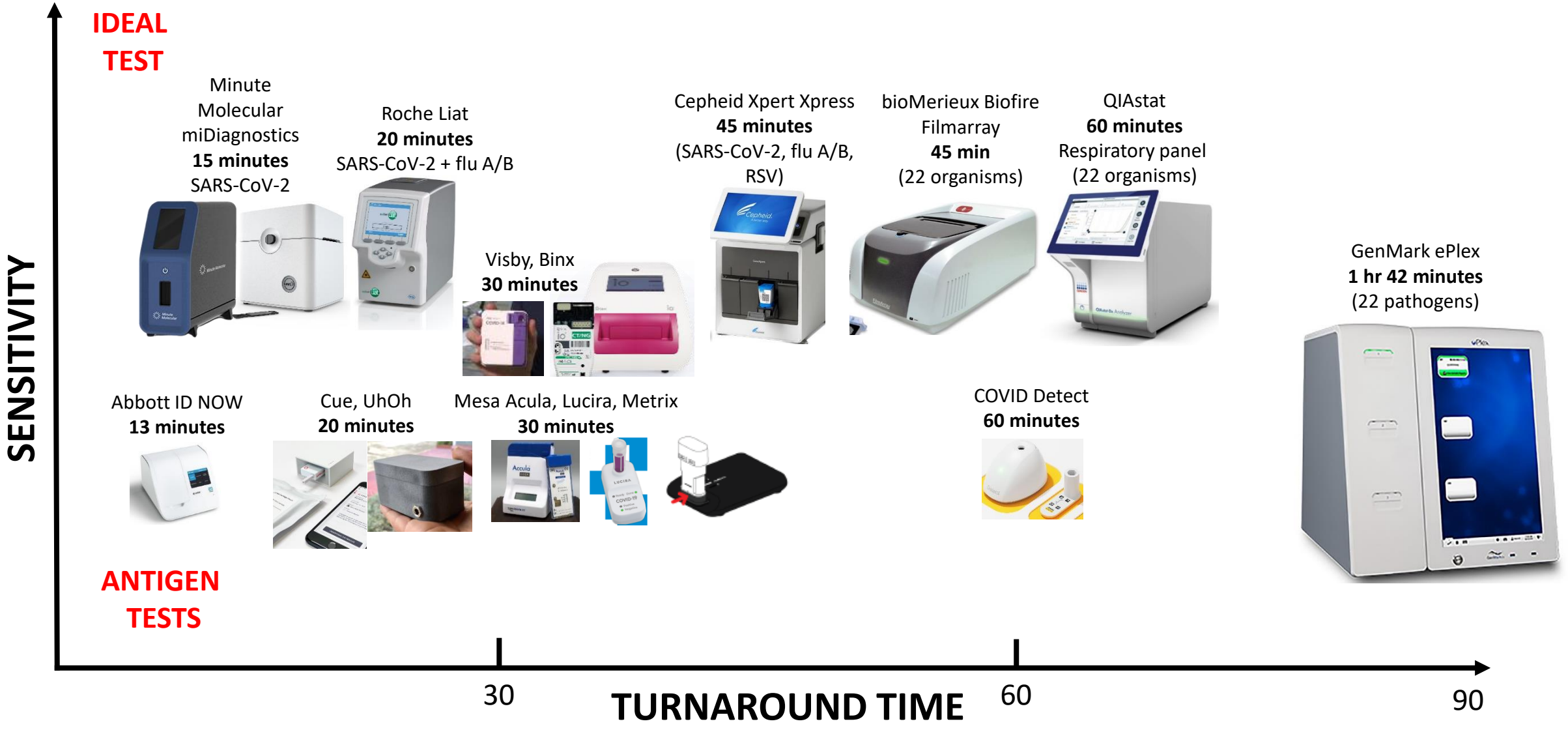
- 6 billion tests produced
- >50 EUA's: OTC, Antigen, Molecular
- 1st over-the-counter home-use test

Shifting the Paradigm

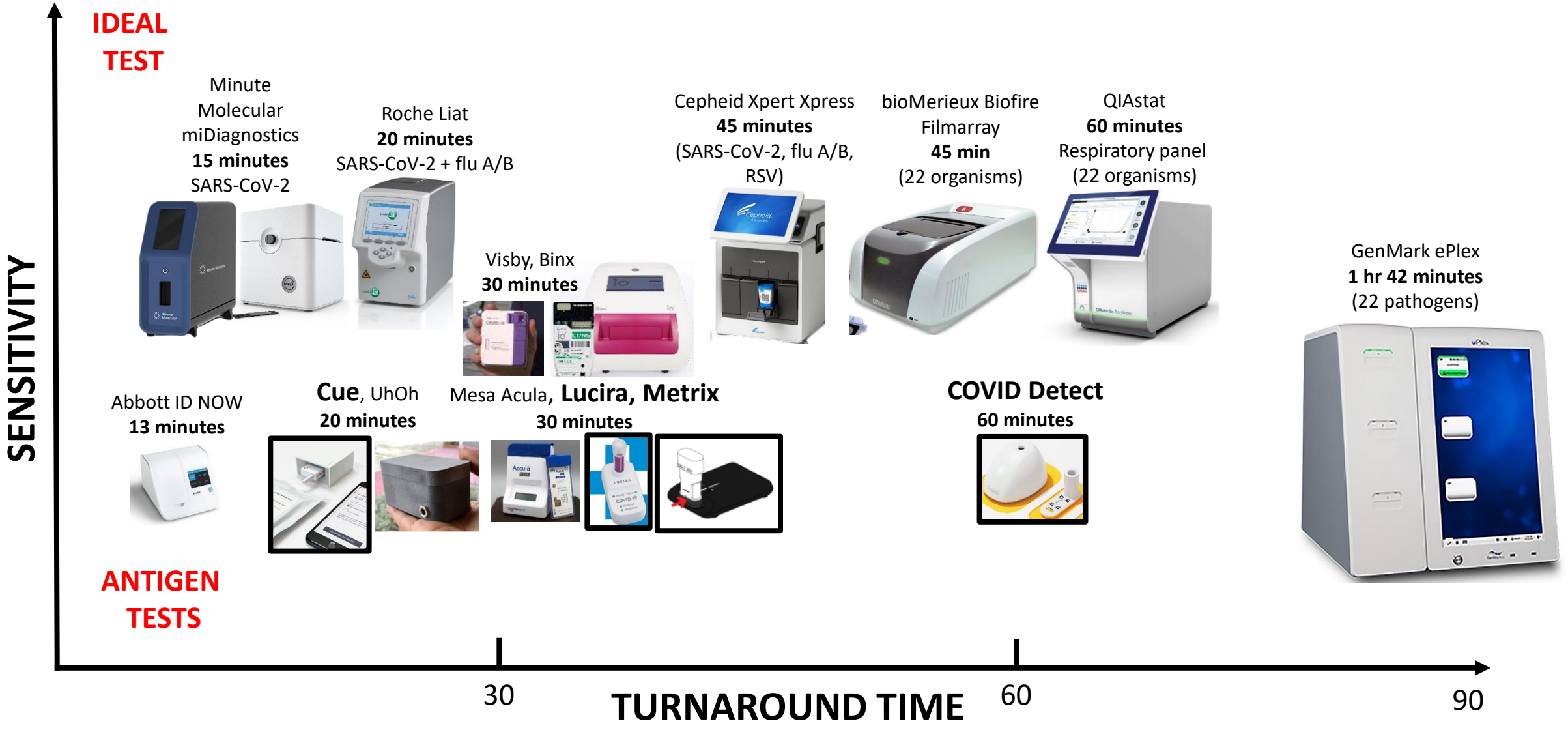
Public >>Private ➡ **Private**>>Public

Lab >>POC ➡ **OTC, POC** >>LAB

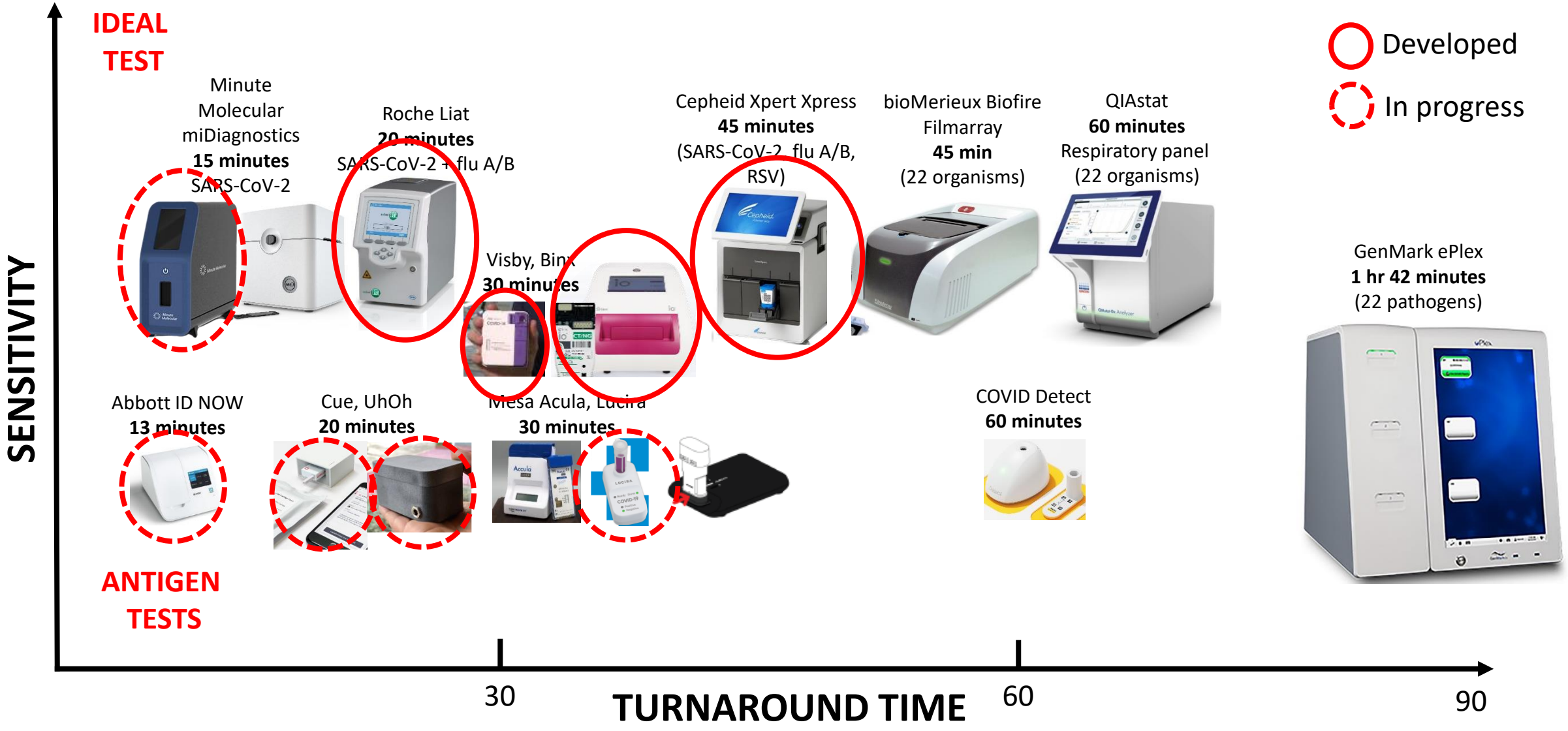
Automated POC Molecular Testing Platforms



Automated POC Molecular Testing Platforms: OTC



POC Platform Pivot to STI's



Lessons learned from COVID-19 in US

- Public health testing capacity is limited
- Monetary investments can accelerate development (RADx)
- Paradigm shift toward POC/ self-testing (regulatory barriers)
- Mail-in self-collection increased in popularity for STI testing during pandemic times and increased access to testing
- Economies of scale – repurposing platforms for other infectious diseases

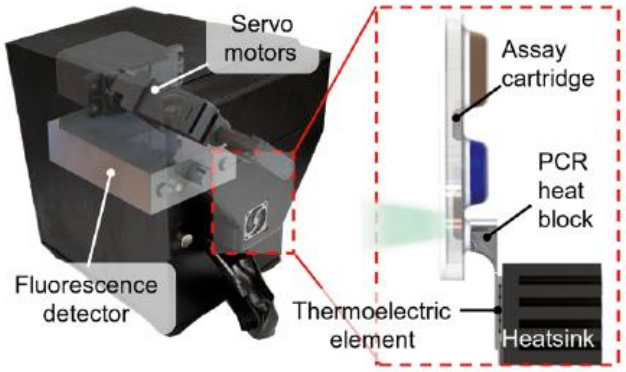
What are the key features for POCT?

- <20 minutes – willingness to wait threshold unless you change clinic workflow
- Easy to perform – able to be performed by paraprofessionals
- Affordable – low cost of goods (COGS) for device and consumables
- Small footprint – many labs in clinics have limited real estate
- Multiplex or parallelization, random access

Widdice LE STD 2018; Gettinger J STD 2020
Robinson M IEEE Open J Eng Med Biol. 2021

Improve Amplification Technology

- Concentration capture sample processing innovation→ Increases sensitivity
  - Membrane filtration, magnetic bead processing[1]
  - Could pair well with LFA or isothermal approaches that are often less sensitive (LAMP, HDA, RPA, CRISPR, endonuclease)
- Increase speed of PCR to decrease TAT – rapid heating and cooling (15 min)
  - MobiNAAT – miniaturization of heat block minimizing thermal mass[2]
  - Dash (Minute Molecular)
- Multiplex – multiple pathogens or AMR detection
  - Novel probe design; melt curve analysis; ratiometric fluorescence detection
- Simplify the read-out – paper LFA after amplification



loop-mediated amplification LAMP, helicase-dependent amplification HDA, Recombinase polymerase amplification RPA,

[1]Credle J Mod Pathol 2021; [2]Trick A, Sci Transl Med 2021 Hsieh K Lab Chip 2022

Trade-offs: Speed, Sensitivity, Cost, Eco Footprint

Lateral Flow Assays

Lower sensitivity
Low cost

Isothermal One-Pot

LAMP, CRISPR, endonuclease

Intermediate sensitivity
Intermediate cost

Molecular POC PCR

High sensitivity
High cost
Now MUCH faster

Kersh EN J Clin Microbiol 2021

Innovation

Lateral Flow Assays

Lower sensitivity
Low cost

↓

Increase signal-to-noise

Increase time of antibody antigen interaction
Electrical resistance detection (faster)
Increase surface area for capture (nanotubes)
Amplify signal
Concentration of larger volume

Isothermal One-Pot

LAMP, CRISPR, endonuclease

Intermediate sensitivity
Intermediate cost

↓

Bring down cost of goods

new isothermal technology-RPA
lateral flow output + battery → OTC

Molecular POC PCR

High sensitivity
High cost

↓

Suitable to context
Lower consumable costs

Less plastic
lateral flow output + battery → OTC

Issues Remaining

Lateral Flow Assays

Lower sensitivity
Low cost

↓

Adds cost and/or time
No reporting for surveillance

Isothermal One-Pot

LAMP, CRISPR, endonuclease

Intermediate sensitivity
Intermediate cost

↓

Still expensive
Often has a smartphone or GUI that may not work in RLS

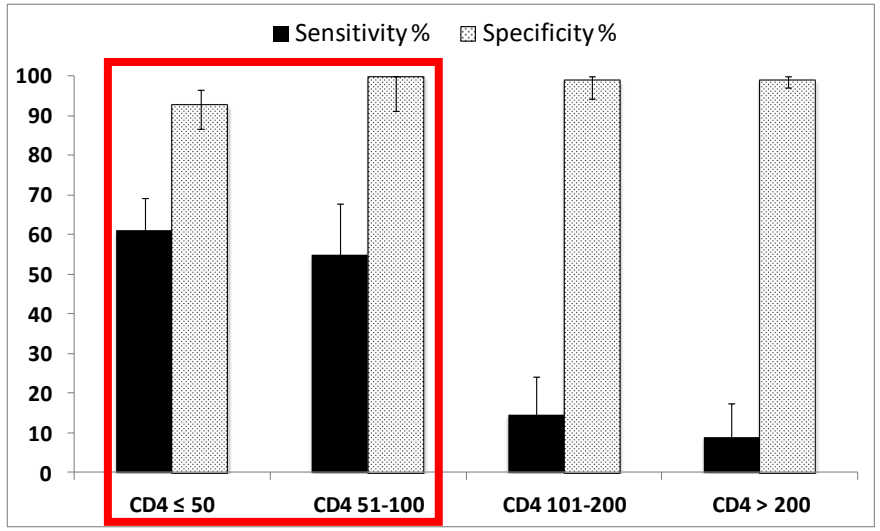
Molecular POC PCR

High sensitivity
High cost

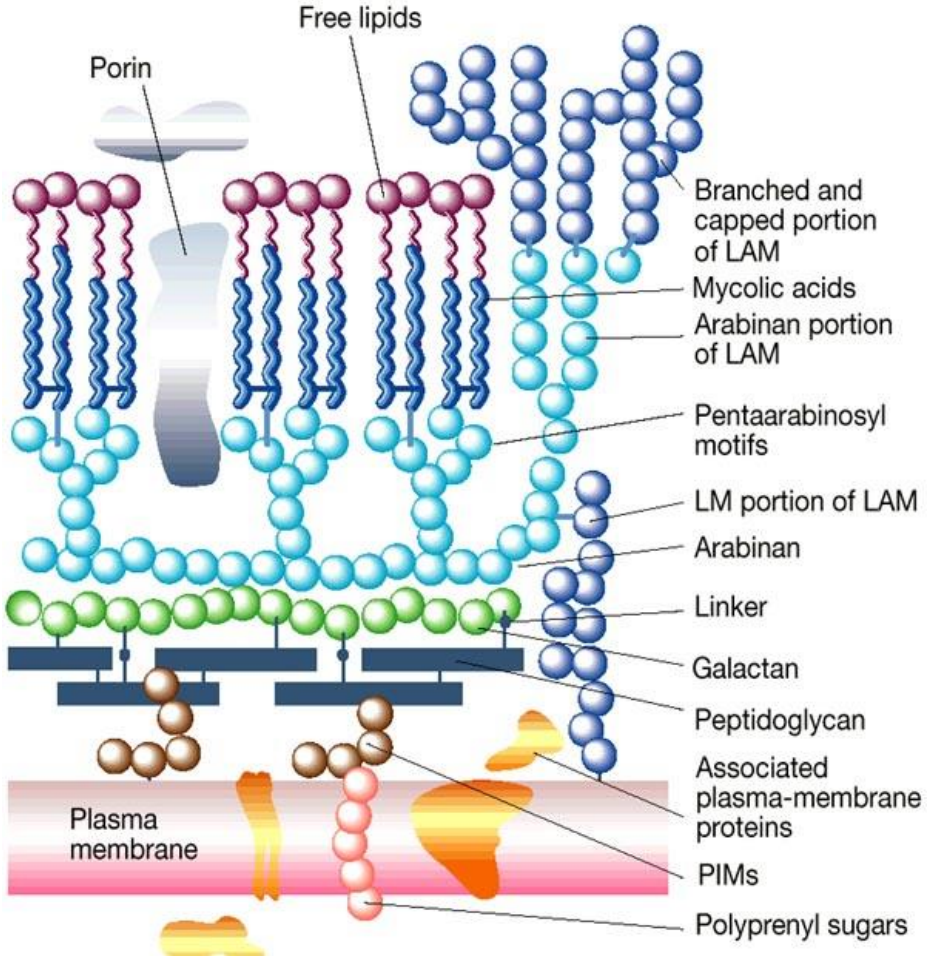
↓

Generates a lot of trash
Needs continuous electricity
Often very expensive if all-in-one (no device)

Cautionary Tale: TB LAM Detection

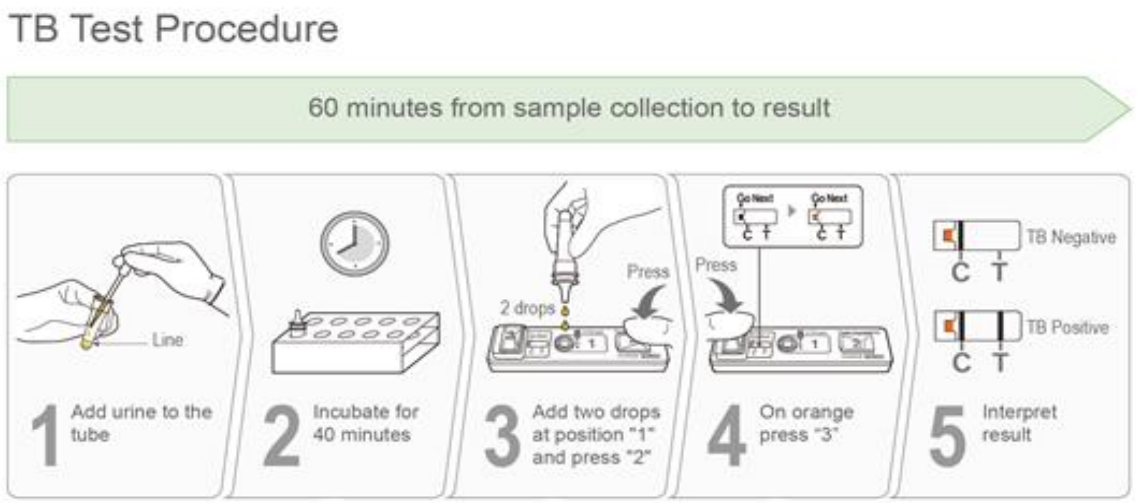


- Drop of urine on LFA → Results in 25 minutes
- Room temperature storage, easy transport
- Individualized foil strip packaging
- Inbuilt procedural control
- DETECTS DISSEMINATED INFECTION in very immunocompromised HIV



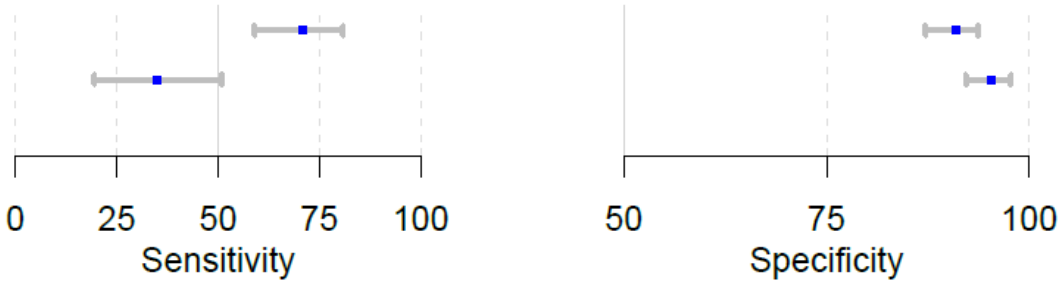
Shah M JAIDS 2009; Lawn SD Lancet Infect Dis 2012; Nakiyingi L JAIDS 2014

Cautionary Tale: FujiLAM



Results in **60 minutes**
Multi-step, more hands-on time
Silver amplification immunochromatography
Limit of detection is ≥30pg LAM/ml urine
30-fold lower cut-off **MORE SENSITIVE**
Production issues→ less specific

Test	N	TP	FP	FN	TN	Sn	[95% CI]	Sp	[95% CI]
FujiLAM	1595	541	76	183	795	70.7	[59.0 – 80.8]	90.9	[87.2 – 93.7]
AlereLAM	1595	307	41	417	830	34.9	[19.5 – 50.9]	95.3	[92.2 – 97.7]
Diff Sn and Diff Sp						35.8		−4.4	



Shah M JAIDS 2009; Lawn SD Lancet Infect Dis 2012; Nakiyingi L JAIDS 2014; Broger T PLoS Med 2020Broger T J Clin Invest 2021

Generation 4

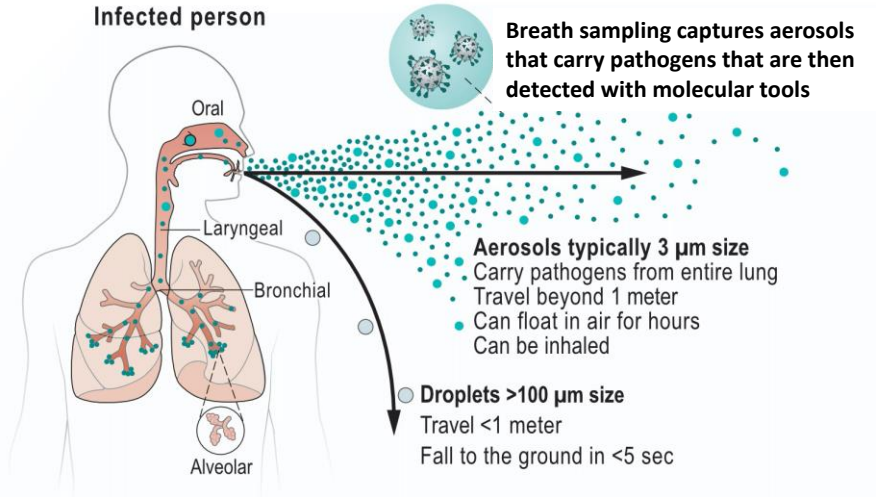
…New approaches…innovation

Beyond Amplification Technology

- Improve Performance
  - Increase signal to noise to achieve high sensitivity- nanotubes
  - Leveraging the decreasing cost of sequencing to detect multiple pathogens and variants[1]
  - Assays that assess host response (VirScan)[3]
- Pheno-molecular approaches to AMR[4]
  - Brief antibiotic exposure prior to quantitative detection of nucleic acid (NAAT)
  - Overcomes need to know the exact genetic basis of resistance
  - Can also target mRNA transcription

[1]Wong KH Curr Protocols in Molecular Biol 2013, Hoff K Langmuir 20216; [2]Karthikeyan S Nature 2022; [3]Xu GJ Science 2015; [4]Savela ES PLoS Biology 2020

Breath Aerosol – TB, COVID-19



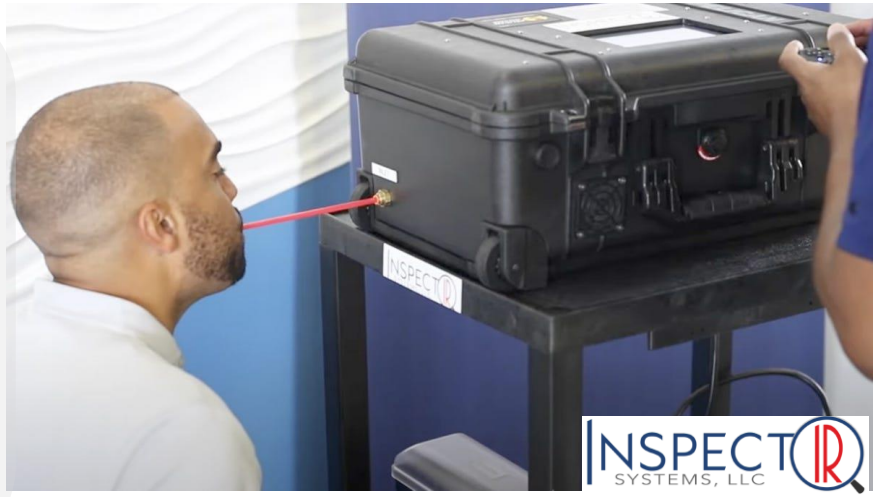
Breath sampling captures human aerosols that carry pathogens. After collection the pathogens' DNA or RNA is detected. (Adapted from Wang.Science.2021;373(6558):eabd9149)

	Initial screening		6-week follow-up						20-week follow-up			
	Sputum sample	Face-mask sample	Sputum sample	Face-mask sample	Chest radiography	Bronchoalveolar lavage result	PET-CT	Outcome	Sputum sample	Face-mask sample*	PET-CT	Outcome
2	–	+	–	+	–	–	–	Treatment withheld and observed	–	–	–	Alternative diagnosis made
3	–	+	+	+	–	+	+	Tuberculosis treatment commenced	–	–	–	Completed treatment
7	–	+	+	+	–	+	+	Tuberculosis treatment commenced	–	–	–	Completed treatment
13	–	+	+	+	–	–	+	Tuberculosis treatment commenced	–	–	–	Completed treatment
17	–	+	+	+	–	–	+	Tuberculosis treatment commenced	–	–	–	Completed treatment

- Non-invasive sampling methods (face mask)
- Link to infectiousness and transmission- TB

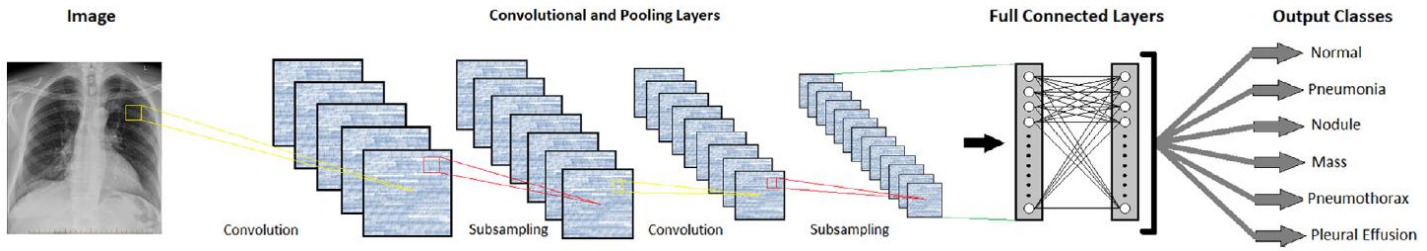
COVID-19: **Received EUA**

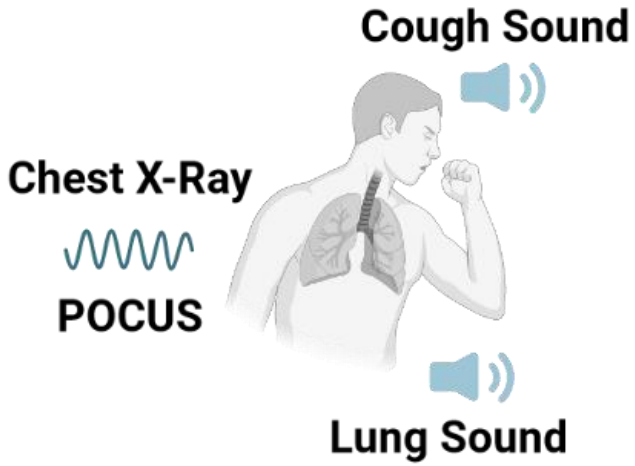
- Volatile organic compounds (VOCs) measured by mass spectrometry
- Symptomatics sensitivity 97.8% specificity 99.1%; asymptomatics sensitivity 91.2%; specificity 99.1%



Williams CM et al, Lancet ID 2020

Artificial Intelligence-Based Diagnostics

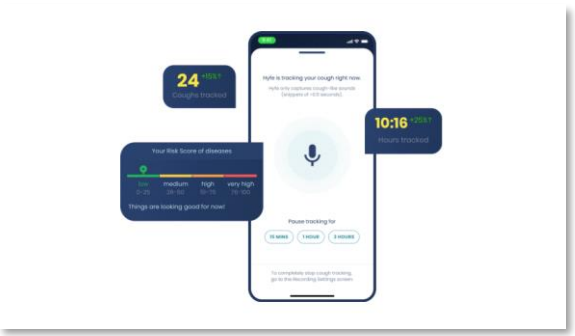




CAD

POCUS

e-Stethoscopes

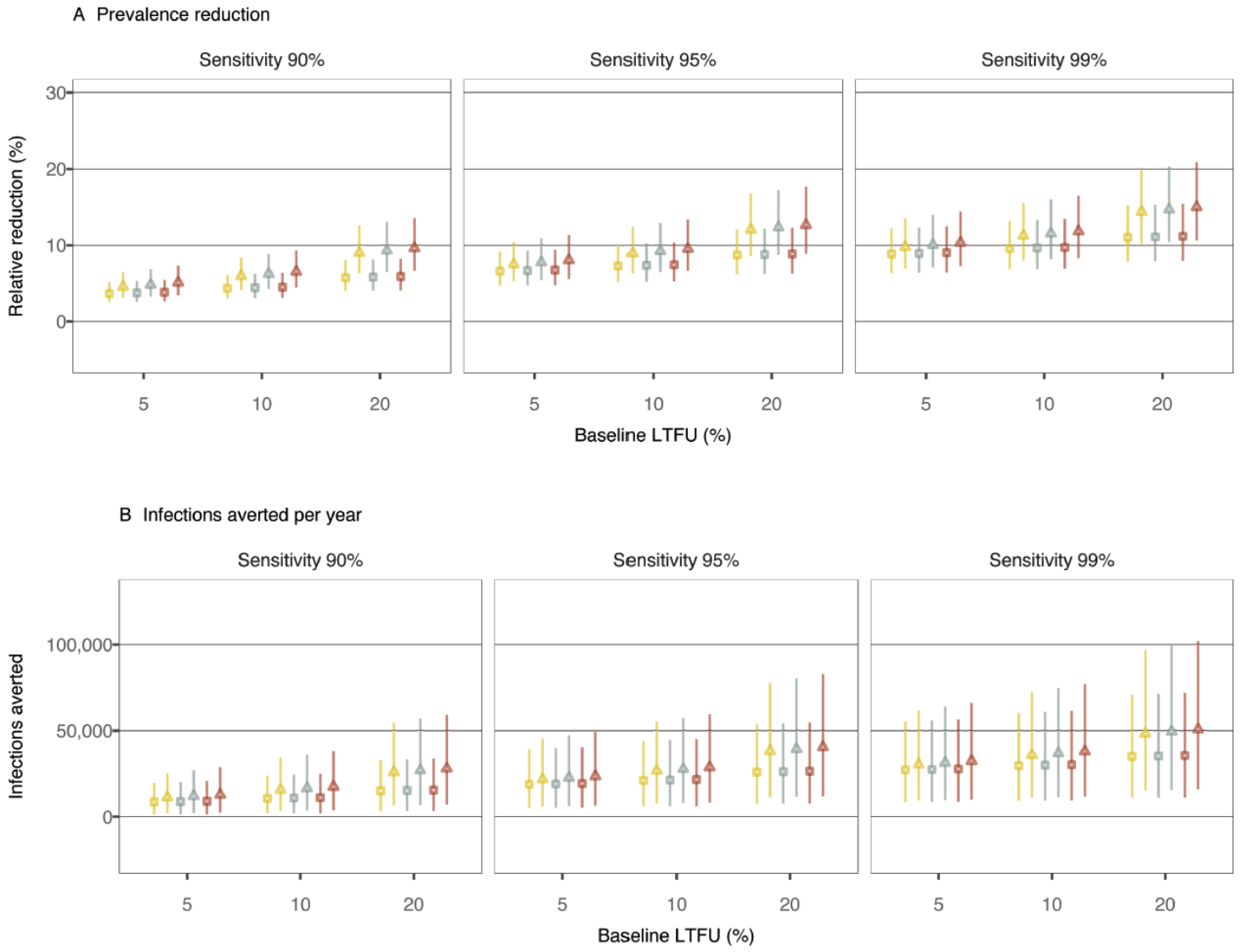


Cough Apps

References: https://onlinelibrary.wiley.com/doi/epdf/10.1111/1754-9485.13273;

“A test that is never performed has 0% sensitivity.”

--Kevin Delaney



- Used a transmission model of chlamydia in the US.
- Increase screening frequency 20% with a POCT
- Sensitivity analyses: POCT sensitivity 90-99%; baseline LTFU 5-20%; treatment delay 1-3 weeks; proportion treated immediately 30-100%

Development Approaches

	Technology-Driven	Clinical Needs-Driven	Value-Based
What is the motivation?	Innovate	Solve problems	Achieve desired outcomes
What guides development?	Technological capabilities	Technical specifications	Systems-level needs
What are the metrics?	Analytical performance	Clinical performance	Clinical/Process/Economic Outcomes
What perspective matters?	Developer interests	Clinical perceptions	Stakeholder perspectives
How important is context?	Context-free	Cross-context	Context-specific
How is the technology marketed?	Innovation potential	Business Case	Value Proposition
What are the cost considerations?	Development costs	Cost of test/device	Total cost
What is the main adoption issue?	Finding clinical champions	Integrating test into workflow	Integrating test into care pathway
What informs purchasing?	Health Technology Assessment	Traditional Procurement	Value-Based Procurement

Adopters are making value-based decisions

Korte B, Point Care, 2020 19(3):77-83

The *Lancet* Commission on diagnostics: transforming access to diagnostics

Kenneth A Fleming, Susan Horton, Michael L Wilson, Rifat Atun, Kristen DeStigter, John Flanigan, Shahin Sayed, Pierrick Adam, Bertha Aguilar, Savvas Andronikou, Catharina Boehme, William Cherniak, Annie NY Cheung, Bernice Dahn, Lluis Donoso-Bach, Tania Douglas, Patricia Garcia, Sarwat Hussain, Hari S Iyer, Mikashmi Kohli, Alain B Labrique, Lai-Meng Looi, John G Meara, John Nkengasong, Madhukar Pai, Kara-Lee Pool, Kaushik Ramaiya, Lee Schroeder, Devanshi Shah, Richard Sullivan, Bien-Soo Tan, Kamini Walia

- 47% of the global population has little to no access to diagnostics
- Democratization of diagnostics will empower patients
- Affects major global health priorities: universal health coverage, antimicrobial resistance, and global health security

“Innovation without access is not innovation at all.”

Oct 6, 2021 Lancet Commission

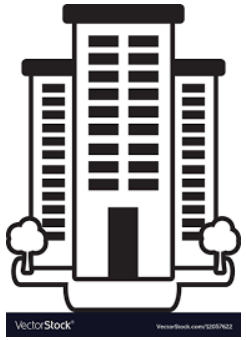
Frugal Innovation – Cost-Conscious Optimization

- **[R**: real-time connectivity]
- **E**: ease of specimen collection, environmental friendliness
- **A**: affordable
- **S**: sensitive
- **S**: specific
- **U**: user-friendly
- **R**: rapid
- **E**: equipment-free
- **D**: delivered

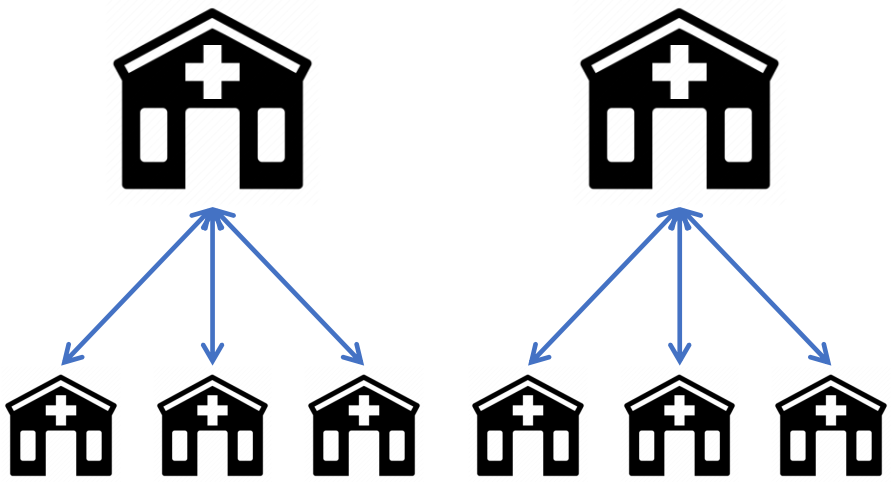
- **Low cost without compromising quality**
- **Consideration of cost of goods up front**

Land KJ Nat Microbiol 2019; Mabey D Nat Rev Microbiol 2004;

Resource-Limited Settings: Not Monolithic



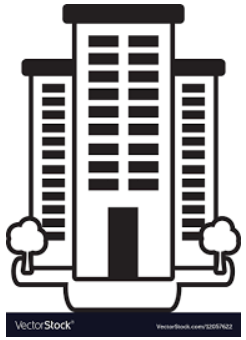
High Throughput
High complexity
Surveillance
Public Health



Unreliable electricity
Medium throughput
Skilled Human resource
Unreliable supply chain

Individual diagnosis
Low price/test
Low infrastructure

Resource-Limited Settings: Not Monolithic



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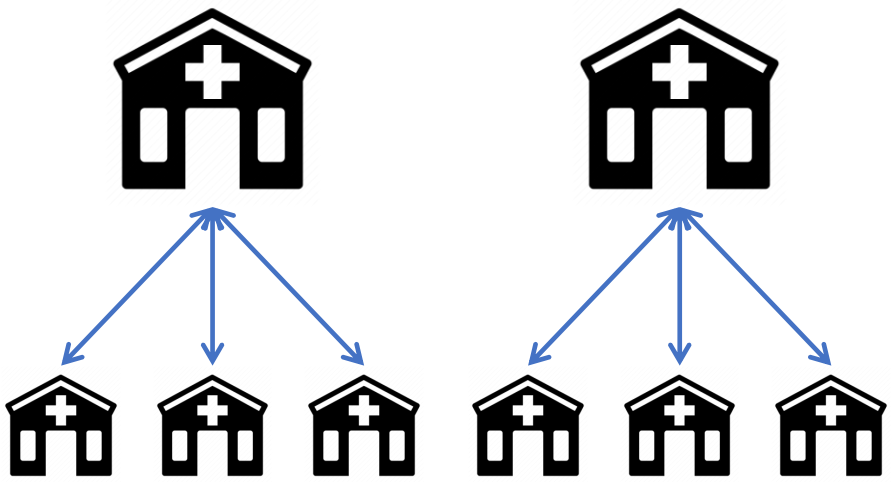

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Consideration for USE CASE should be made early together with clinicians…
…this is often missing in medtech development

Unraveling the Gordian Knot: Using POC Assays to Improve Public Health

- Incentivize pivoting platforms from COVID-19 to other infectious diseases (RADx)
- Move true ‘beyond PCR’ innovation from proof-of-concept to commercialization
- RLS in both US and in LMIC will need cost-effective solutions to improve access to diagnostics

https://uxdesign.cc/unraveling-a-complex-ux-problem-how-a-greek-myth-helped-me-conquer-information-architecture-743ebd7d0ea


Life is not about waiting for the storm to pass, but learning to dance in the rain

Acknowledgements

POCTRN

Rapid Acceleration of Diagnostics (RADx)

CIMIT®
Consortia for Improving Medicine with Innovation & Technology

ACME POCT

UMASS LOWELL • WORCESTER M2D2
Advancing Med Device & Biotech Innovations

CAPCaT
Center for Advancing Point of Care Technologies

C-THAN

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Center for Innovative Diagnostics for Infectious Diseases

Maunank Shah
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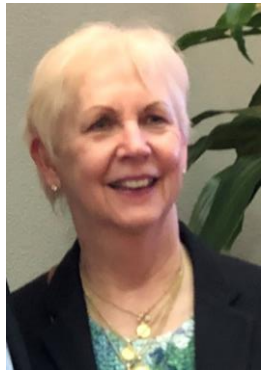
Matthew Robinson
Johan Melendez
Justin Hardick
Jeffrey Holden

Claudia Denkinger



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NIH National Institutes of Health
Office of Behavioral and Social Sciences Research

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