Rapid Acceleration of Diagnostics: *RADx (Tech + ATP)*

Bruce J. Tromberg, Ph.D.
Director, National Institute of Biomedical Imaging and Bioengineering (NIBIB)

National Institute of Biomedical Imaging and Bioengineering

RADx Tech & ATP

NIH Office of the Director

Francis Collins

Rachael Fleurance

Larry Tabak

Tara Schwetz

April 29

RADx Tech – $500M

Highly competitive, rapid three-phase challenge to identify the best co … for at-home or point-of-care tests for COVID-19

RADx Advanced Technology Platforms (RADx-ATP) – $230M

Rapid scale-up of advanced technologies to increase rapidity and enhance and validate throughput – create ultra-high throughput machines and facilities

RADx Radical (RADx-Rad) – $200M

Develop and advance novel, non-traditional approaches or new applications of existing approaches for testing

RADx Underserved Populations (RADx-UP) – $500M

Interlinked community-based demonstration projects focused on implementation strategies to enable and enhance testing of COVID-19 in vulnerable populations

April 24, 2020: $1.5B to NIH
$500 Million to NIBIB

Jill Heemskerk.

Bruce Tromberg

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

BARDA

$307 M Partnership with BARDA

OASH

Tech/ATP Team Leads: Tiffani Lash, Todd Merchak, Taylor Gilliland, Kate Egan, Mike Wolfson, Doug Sheeley, Gene Civillico

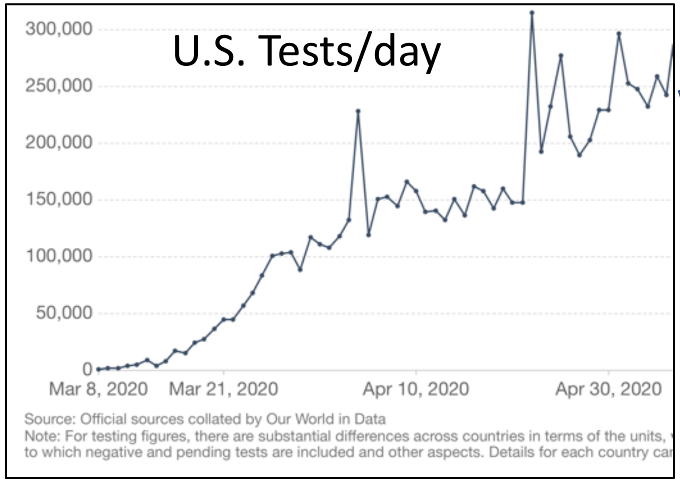
https://www.nih.gov/research-training/medical-research-initiatives/radx;
Tromberg, Collins et al. NEJM, 2020

RADx Tech & ATP Goals

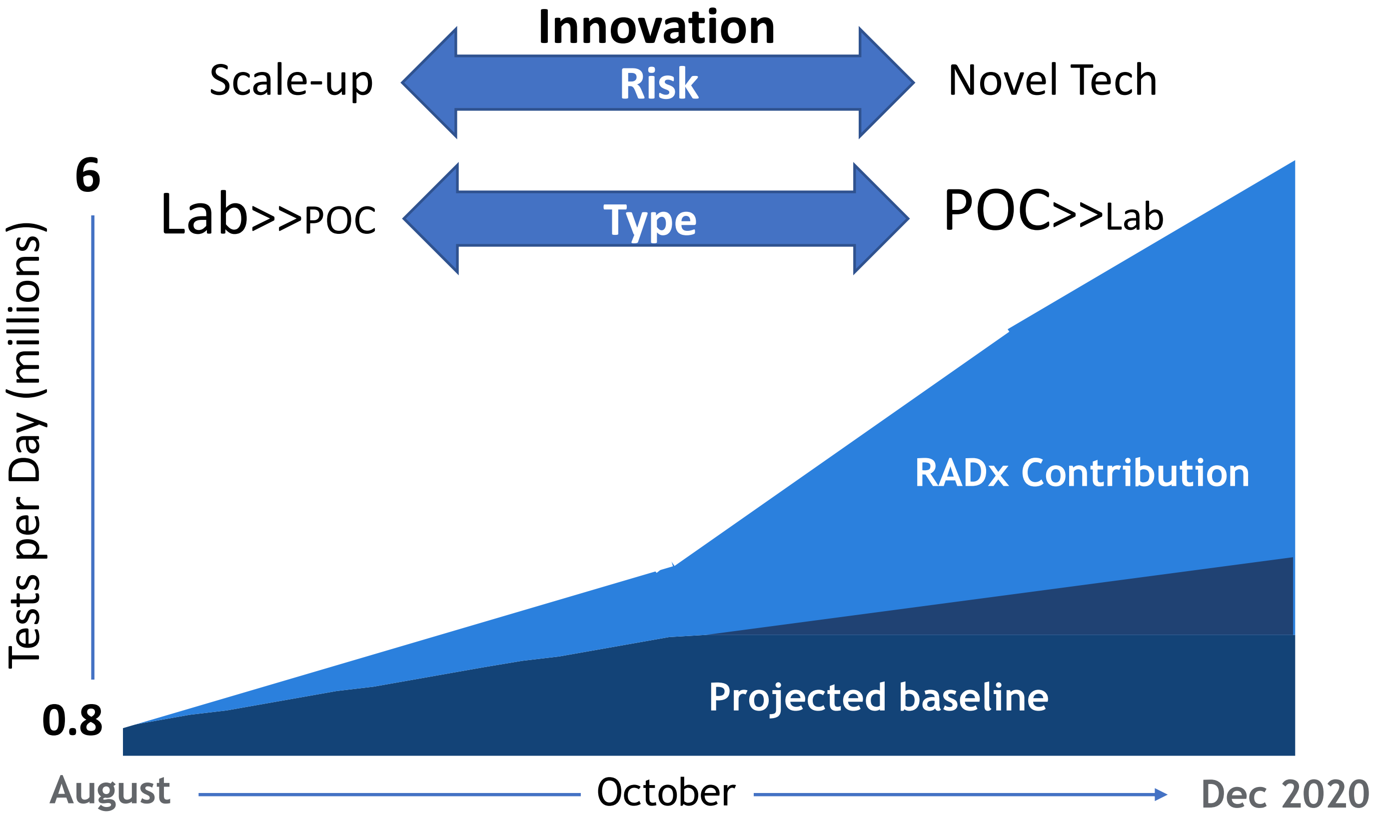
1) Expand COVID-19 Testing Technologies: *Number, Type and Access*
2) Optimize Performance: *Technologic and Operational; Match Community Needs*

Test Settings

- Home-based
- Point of Care (POC)
- Laboratory (CLIA, research)



RADx
Launch:
~250k/day



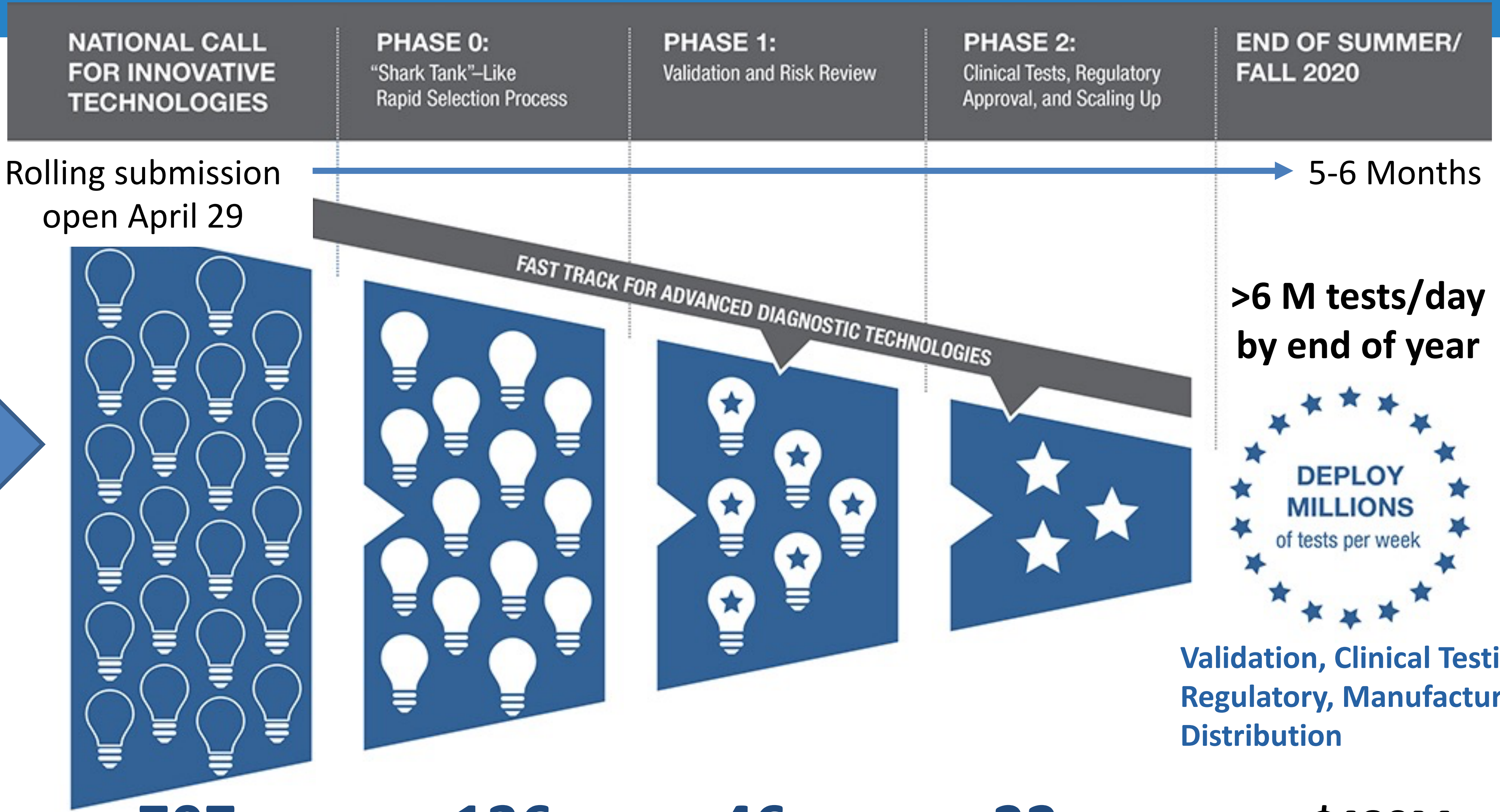
RADx Tech/ATP Innovation Funnel

Applications Started

~3000

Rolling submission open April 29

5-6 Months



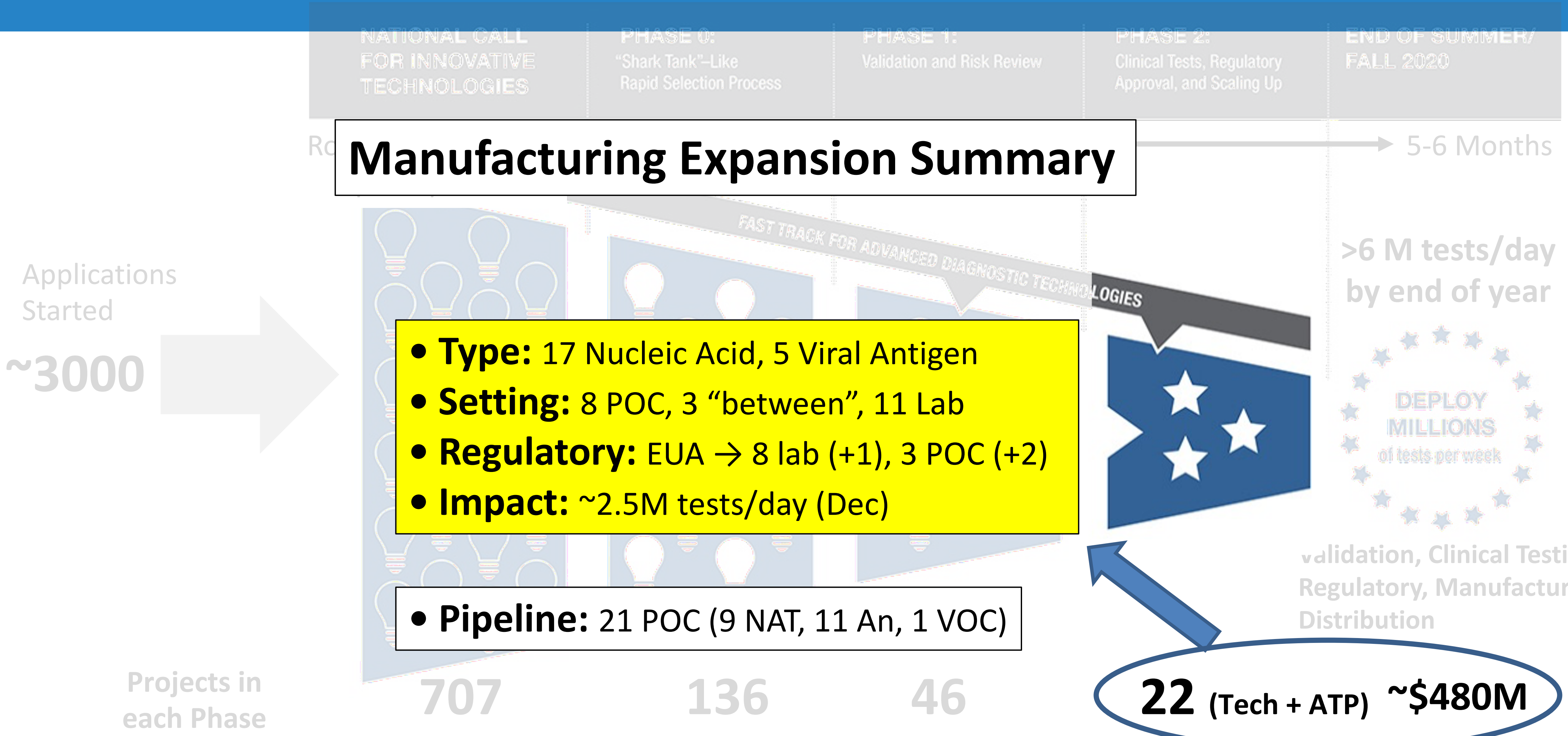
>6 M tests/day by end of year

Validation, Clinical Testing, Regulatory, Manufacturing, Distribution

Projects in each Phase

707 **136** **46** **22** **(Tech + ATP)** **~$480M**

RADx Tech/ATP Innovation Funnel



Manufacturing Expansion Summary

- **Type:** 17 Nucleic Acid, 5 Viral Antigen
- **Setting:** 8 POC, 3 "between", 11 Lab
- **Regulatory:** EUA → 8 lab (+1), 3 POC (+2)
- **Impact:** ~2.5M tests/day (Dec)

- **Pipeline:** 21 POC (9 NAT, 11 An, 1 VOC)

22 (Tech + ATP) **~$480M**

22 Manufacturing Expansion

Innovation

1) Separation/concentration
2) µ-Fluidics
3) Chemistries, e.g. CRISPR, NGS
4) Labels, Reporters
5) Readout Tech
6) Miniaturization
7) Automation

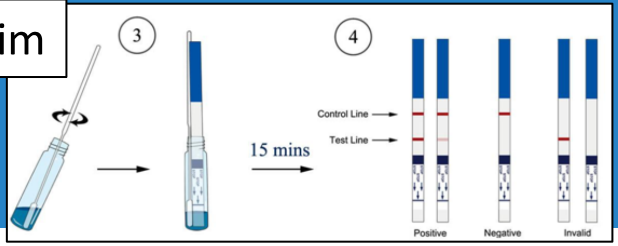
Visby Medical	Nucleic Acid: RTPCR	**POC**
MicroGEM International	Nucleic Acid: RTPCR	**POC**
Mesa Biotech, Inc.	Nucleic Acid: RTPCR	**POC**
Talis Biomedical Corp.	Nucleic Acid: Isothermal PCR	**POC**
MatMaCorp	Nucleic Acid: RTPCR	**Lab/POC**
Ubiquitome	Nucleic Acid: RTPCR	**Lab/POC**
Maxim Biomedical Inc	**Antigen: LFA dipstick**	**POC**
Luminostics, Inc.	**Antigen: LFA**	**POC**
Ellume USA LLC	**Antigen: LFA**	**POC/home**
Quidel Corp.	**Antigen: LFA**	**POC**
Quanterix	**Antigen/microbeads**	**Lab**
Mammoth Biosciences	Nucleic Acid: CRISPR	**Lab**
Flambeau Diagnostics	Nucleic Acid: Isothermal PCR	**Mobile Lab**
Ceres Nanosciences Inc	Nucleic Acid: Extraction	**Lab**
Fluidigm	Nucleic Acid: RTPCR	**Lab**
Broad Institute	Nucleic Acid: RTPCR	**Lab**
Illumina Inc	Nucleic Acid: NGS	**Lab**
Helix OpCo, LLC	Nucleic Acid: NGS	**Lab**
Ginkgo Bioworks	Nucleic Acid: NGS	**Lab**
Sonic Healthcare USA	Nucleic Acid: RTPCR	**Lab Network**
PathGroup	Nucleic Acid: RTPCR	**Lab Network**
Aegis Sciences	Nucleic Acid: RTPCR	**Lab Network**

Tens to 100,000 tests/day

https://www.nibib.nih.gov/covid-19/radx-tech-program/radx-tech-phase2-awards

Mesa BioTech

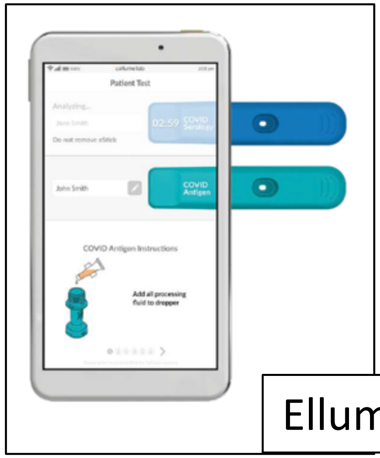
Maxim



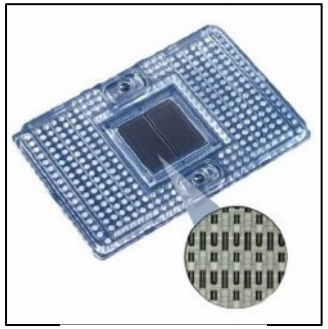
Quidel Sophia

Visby Medical

Ubiquitome



Ellume



Fluidigm

Luminostics

Flambeau

Visby Medical	Nucleic Acid: RTPCR	**POC**
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Point-of-Care Technologies Research Network (POCTRN)

NIBIB National Network: ***5-6 years for new POC technologies***

Established 2007, Expanded 2020: >1000 RADx experts & contributors

https://www.poctrn.org


Todd Merchak Tiffany Lash

RADx UP

Duke/UNC CDCC RADx UP Coordinating Center

VENTUREWELL
idea to impact

GaTech/Emory
- ✓Engineering
- ✓Design/Prototype
- ✓Clinical Validation
- ✓Biobank samples
- ✓In-Home Validation

Johns Hopkins
- ✓Public Health/STD
- ✓Global Health
- ✓Clinical Validation
- ✓Biobank samples
- ✓Validation in LMICs

CIMIT/MGH
- ✓Coordinating Center
- ✓Collaboration/Management Platform
- ✓Business/Commercialization

Northwestern
- ✓HIV/AIDS
- ✓Engineering
- ✓Global Health
- ✓Clinical Validation
- ✓Validation in LMICs

UMass
- ✓Heart, lung, blood
- ✓Engineering
- ✓Clinical Validation
- ✓Biobank samples
- ✓Clinical Trials
- ✓Business/Commercialization

CBIOM C3i

Validation Core

Clinical Studies Core

Deployment Core

RADx Leveraging NIH Proof of Concept (PoC) Network


Jodi Black


Matt McMahon

~40 early-stage RADx-tech projects

- Project Funding
- Industry Coaching and Mentoring
- Training and Resources

WASHINGTON ENTREPRENEURIAL RESEARCH EVALUATION & COMMERCIALIZATION HUB
WE-REACH
Bridge to Medical Impact

MBArC MIDWEST BIOMEDICAL ACCELERATOR CONSORTIUM

NCAI-CC NIH Center for Accelerated Innovations at Cleveland Clinic

UC CAI
University of California Center for Accelerated Innovation

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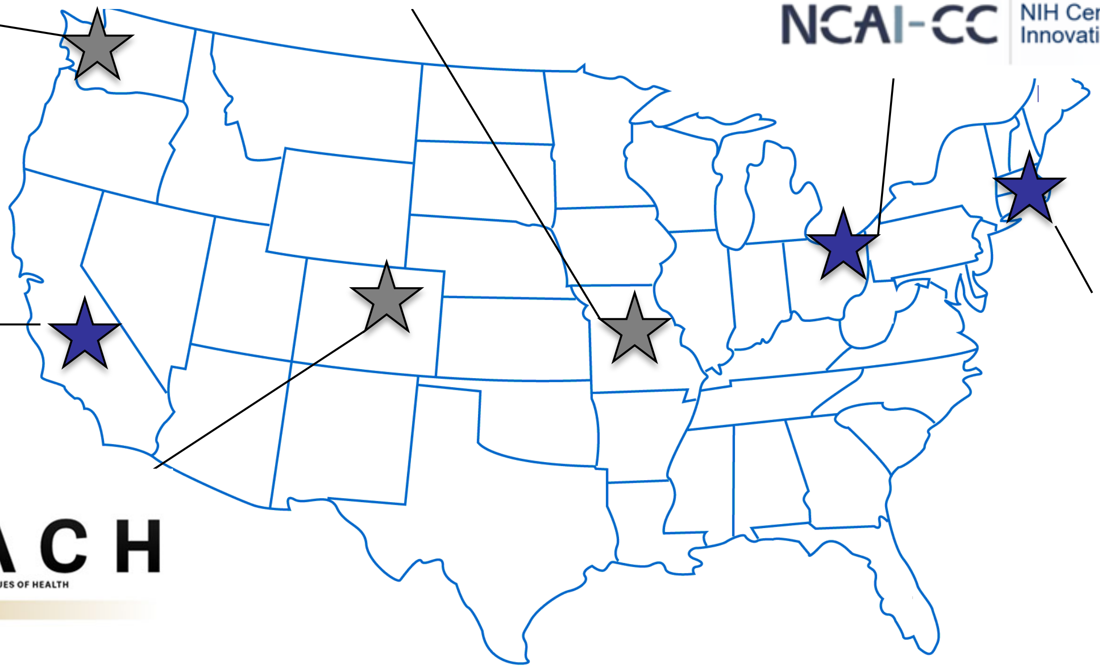


CIMIT®
Consortia for Improving Medicine with Innovation & Technology

B-BIC: Translating Discoveries Into Products

SPARK IS NOW POWERED BY NIH REACH
SPARK REACH
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS
NATIONAL INSTITUTES OF HEALTH
COLORADO

NIH National Institutes of Health
Office of Extramural Research

RADx Test Validation Core (Emory-Gtech)

15 projects complete, 11 ongoing



Wilbur Lam   Greg Martin.   Oliver Brand

Feasibility

- Ensure positive control (provided or commercial) is positive
- Ensure negative matrix (i.e. saliva, patient sample or commercial) is negative
- Ensure negative matrix spiked with live and/or inactivated SARS-CoV-2 virus is positive

↓

Contrived samples

- Verify the limit of detection (LOD) via live and/or inactivated SARS-CoV-2 virus by serial dilution using correct matrix
- Test non-SARS-CoV-2 coronaviruses (test specificity/cross-reactivity)
- Test different strains of SARS-CoV-2 (strain variation)

↓

Patient samples

- Test banked patient samples (adult and pediatric) with concomitant testing on reference method to determine concordance
- Test prospective patient samples using collection sites
- Calculate sensitivity, specificity, positive and negative predictive values with input from our biostatistical core

>1500 participants

RADx Test Validation Core (Emory-Gtech)

15 projects complete, 11 ongoing

Feasibility

- Ensure positive control (provided or commercial) is po
- Ensure negative matrix (i.e. saliva, patient sample or c
- Ensure negative matrix spiked with live and/or inactiva

NIH score range: 1 (exceptional) to 9 (poor)

ACME POCT score: 2 (88% of respondents)

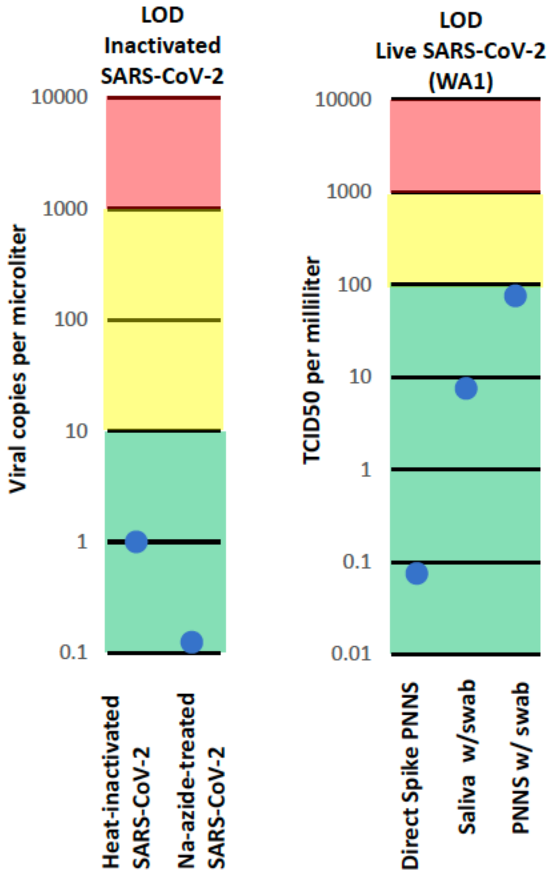
RADx Test Verification Core Recommendation: Proceed to WP2

Resume and Summary of Discussion: the RADx ACME POCT convened an internal study section on July 9th, 2020 to discuss the RADx Test Verification Core's analysis of Project #2244 in which the criteria for evaluation included: LOD, Sensitivity, Specificity, Repeatability, and Usability. The testing of this COVID-19 point-of-care (POC) PCR diagnostic test comprised of 1) LOD testing at several of our sites, including our Emory BSL-3 facility, Children's Healthcare of Atlanta clinical pathology laboratory, and laboratories in

Patient samples

- Test banked patient samples (adult and pediatric) wit
- Test prospective patient samples using collection sites
- Calculate sensitivity, specificity, positive and negative

OVERALL SUMMARY OF RESULTS ACROSS ACME POCT SITES



Specificity	
Virus Type	Lack of Cross-Reactivity?
OC43 seasonal coronavirus	✔
MERS (heat inactivated)	✔

Prospective Clinical Results

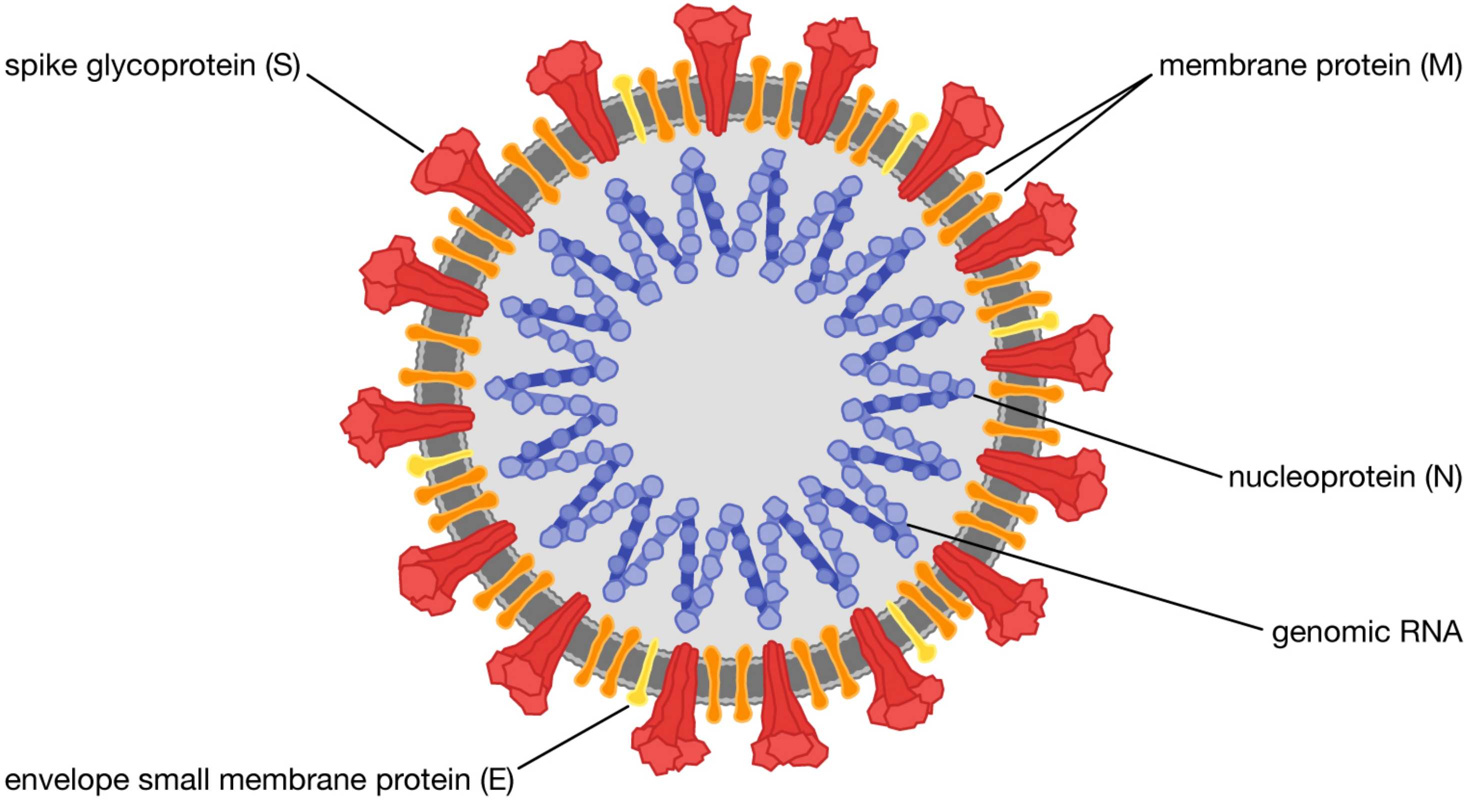
2244	DiaSorin RT-PCR +	DiaSorin RT-PCR -
+	4	0
-	0	48

Sensitivity: 100%
Specificity: 100%

* PNNS, pooled negative nasal swab

RADx Test Validation Core (Emory-Gtech)

Challenge: *Compare NAT and Antigen Test Performance*



Viral Antigen Test
Lateral Flow Assay (LFA)
LOD: $TCID_{50}$/mL ~10^3-10^4/mL

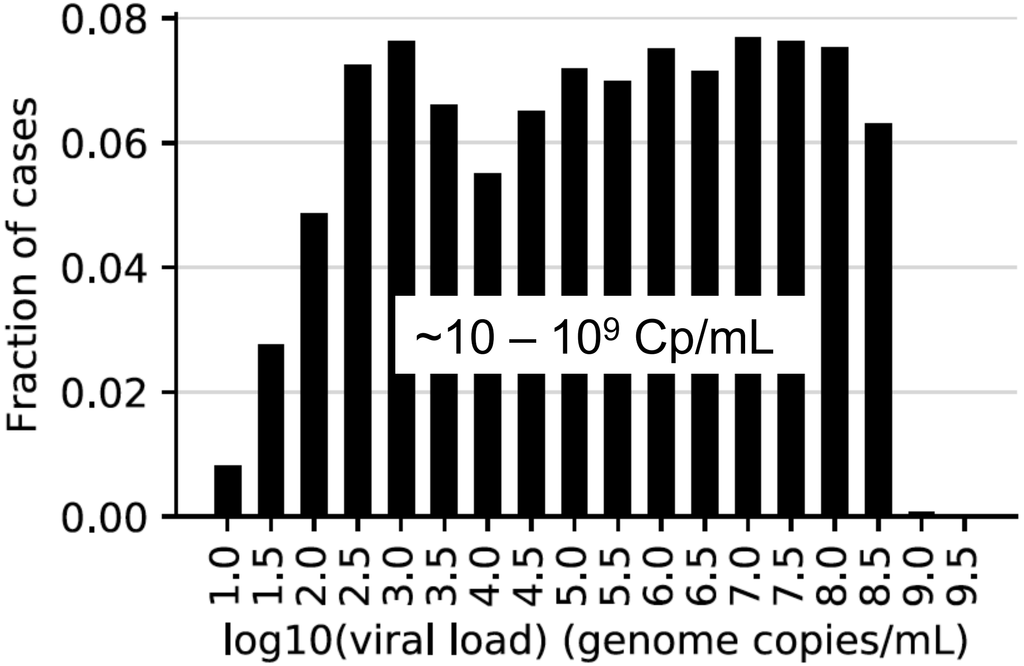
Copies/$TCID_{50}$?

Nucleic Acid Test
RTPCR (Isothermal PCR)
LOD: Cp/mL ~10^2-10^3/mL

Understanding Screening/Surveillance Performance

Impact of LOD and Population Viral Load on Performance

Population Viral Loads from Ct values *(n = 4774)*



Ramy Arnaout, James E. Kirby, et al., **SARS-CoV2 Testing: The Limit of Detection Matters**
bioRxiv 2020.06.02.131144; doi: https://doi.org/10.1101/2020.06.02.131144

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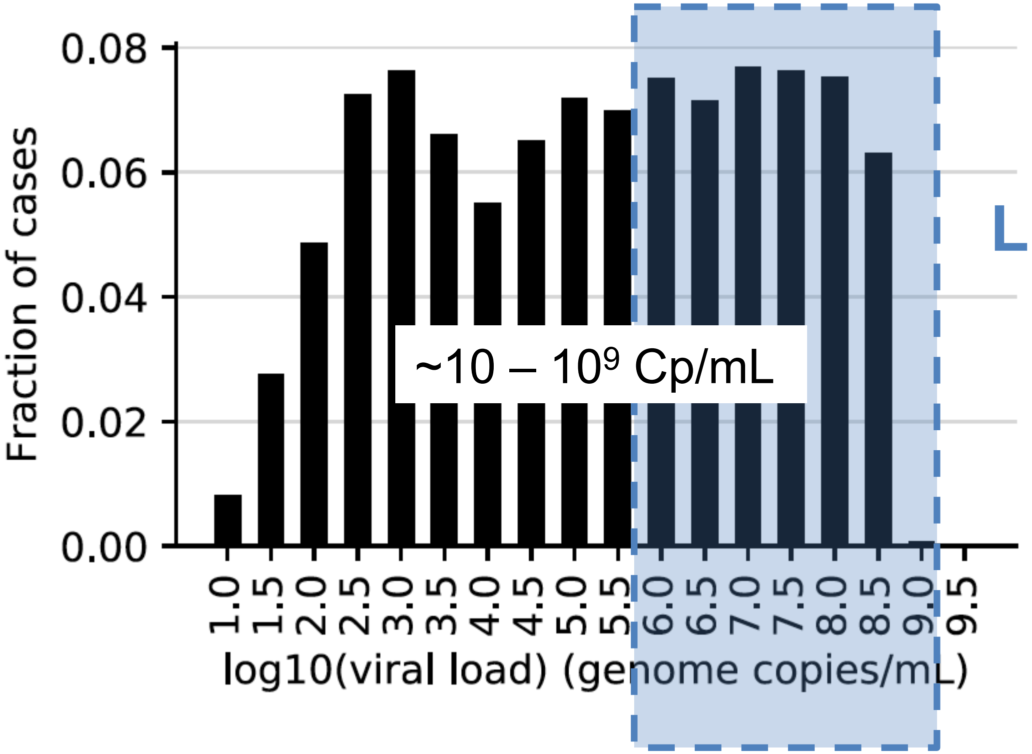

LFA → Typical LOD ~10^6 Copies/mL
Sensitivity ~40% for all population (symptomatic + asymptomatic)

Vs.

Sens/Spec ~90/95% for symptomatic population (EUA: ~5 days onset)

Ramy Arnaout, James E. Kirby, et al., **SARS-CoV2 Testing: The Limit of Detection Matters**
bioRxiv 2020.06.02.131144; doi: https://doi.org/10.1101/2020.06.02.131144

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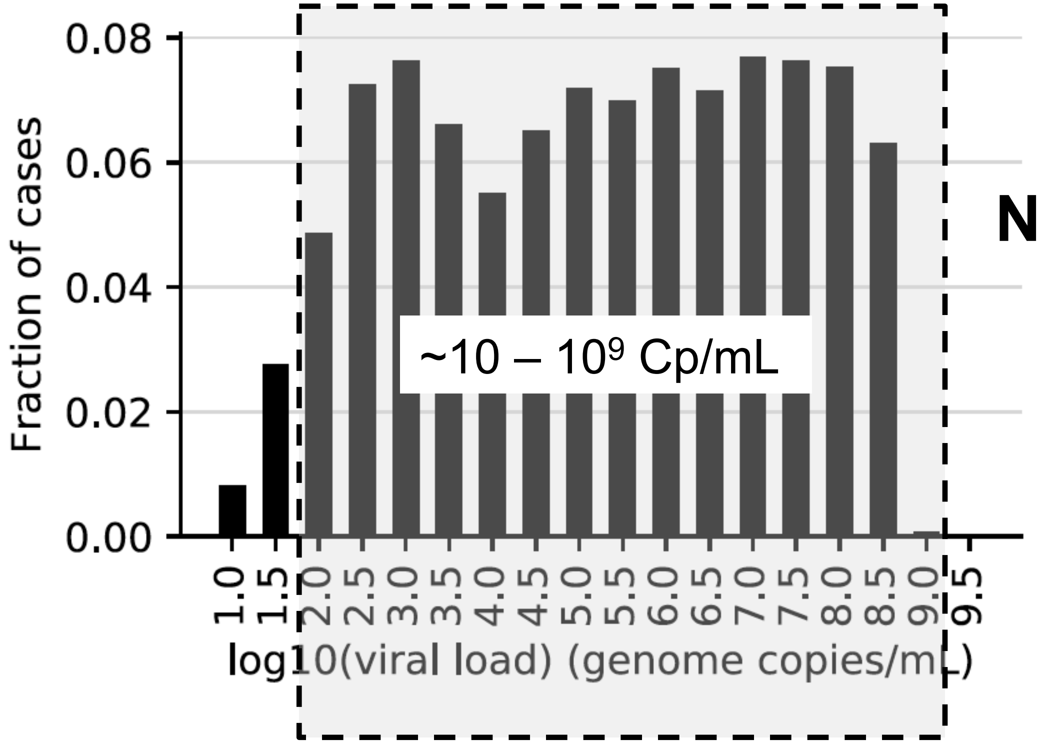


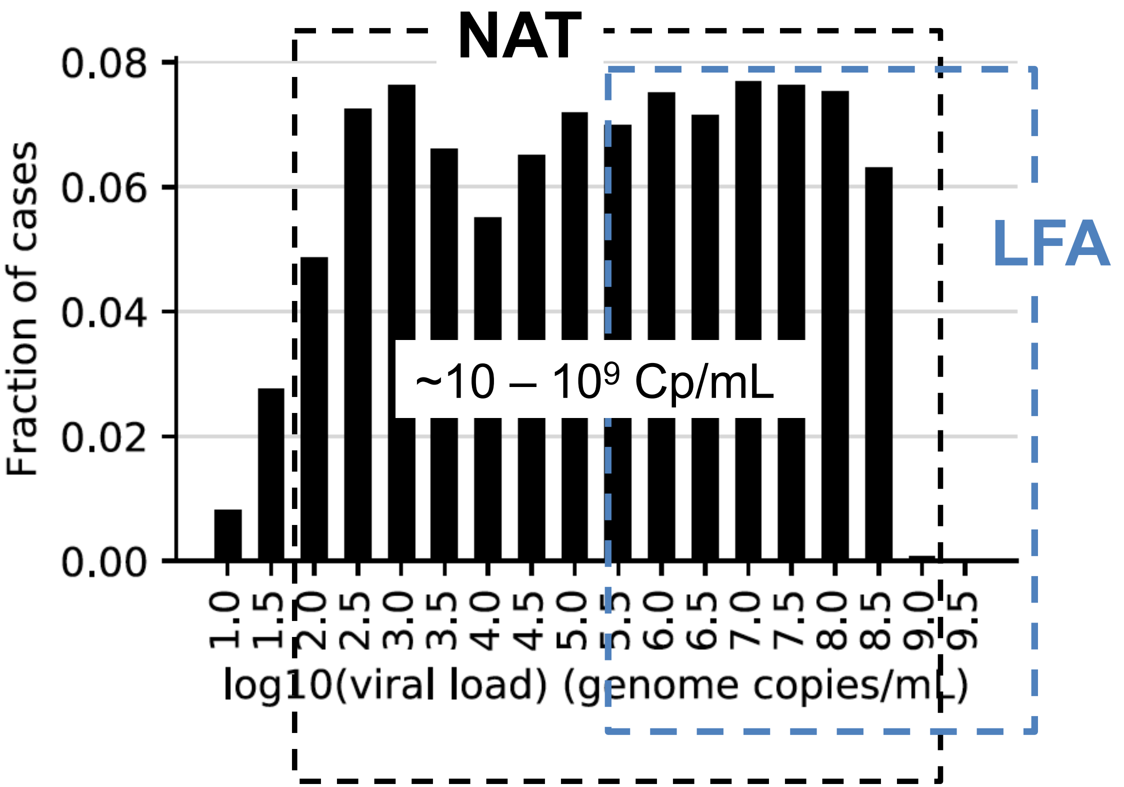
NAT → Typical LOD > ~10^2 Copies/mL
Sensitivity >~90% for all population (symptomatic + asymptomatic)

Ramy Arnaout, James E. Kirby, et al., **SARS-CoV2 Testing: The Limit of Detection Matters**
bioRxiv 2020.06.02.131144; doi: https://doi.org/10.1101/2020.06.02.131144

Understanding Screening/Surveillance Performance

Implications: NAT (PCR) vs LFA (An)

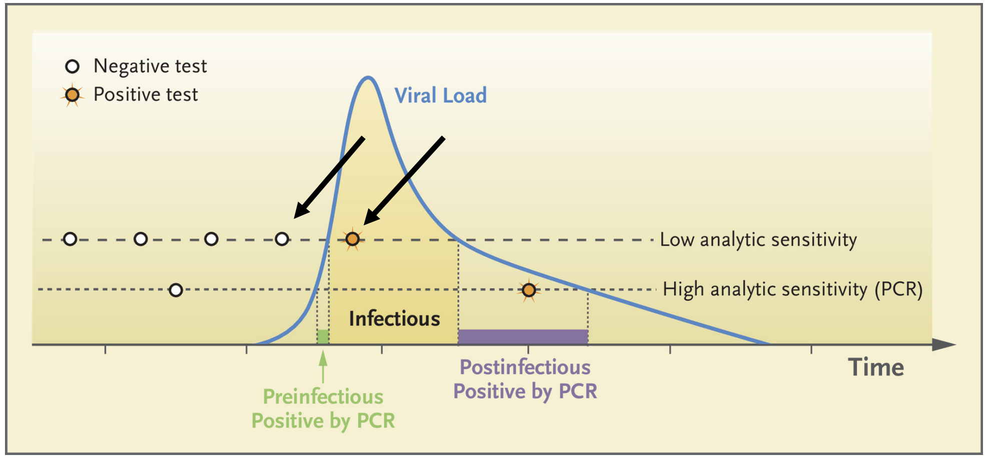
Population Viral Loads from Ct values *(n = 4774)*



1) Use LFA within ~5-7 days of symptoms
   - Elevated viral load (>90% sens, spec)

2) "Off Label" LFA in Asymptomatics:
   - Backup PCR w/positive in low prevalence
   - Backup PCR w/negative recently exposed

3) Sequential LFA tests



Ramy Arnaout, James E. Kirby, et al., **SARS-CoV2 Testing: The Limit of Detection Matters**
bioRxiv 2020.06.02.131144; doi: https://doi.org/10.1101/2020.06.02.131144

M. Mina et al, NEJM, DOI: 10.1056/NEJMp2025631

RADx Clinical Studies Core (UMass)

Mission: Evaluate RADx platforms that advance to Phase 2 in rigorous clinical studies w/ diverse populations and settings.

Standard Trial Design: Master protocols, powered studies (~250 subjects), device-specific amendments, accelerate regulatory review

Eureka Digital Health Platform mobile app and website, participants enter own data

Data Safety Board and Single IRB for oversight and safety monitoring

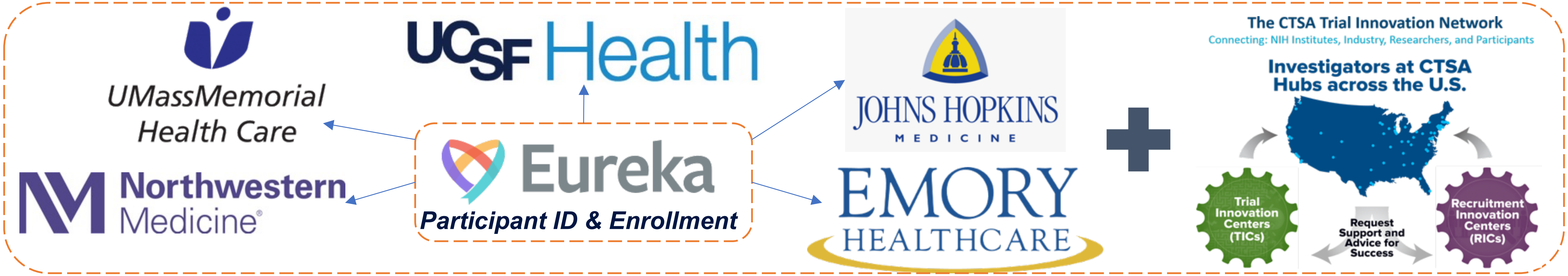
Robust Research Center Network: POCTRN core center network for enrollment (w/Practice Based Research Network and Centers for Clinical and Translational Science assisting)

Laura Gibson, MD

David McManus, MD

COVID-19 Test US

Clinical Study Partners



RADx Deployment Core (CIMIT)

Bridging NIH/USG, non-profit Foundations, Academia, and Industry

Mission

Provide support for successful commercialization and deployment of COVID-19 solutions in unique communities.

- Members: 32
- Nancy Gagliano, MD, Core Lead
- Brian Walsh, Commercialization Lead
- Sreeram Ramakrishnan, Data Solutions Lead
- Susan Moreira, Deployment Lead

Nancy Gagliano, MD

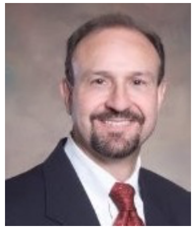
www.poctrn.org
RADx webinars, tools

Current Highlights

- Supply Chain continues to be core challenge
- Development of Testing Model has received international recognition
- User communities need end-to-end solutions to deploy COVID testing
- Design-a-thon scheduled to develop data solutions

"When-to-Test" modeling tool: Match tests w/needs; evaluate impact of risk reducing activities.

Anette Hosoi
MIT



Paul Tessier,
CIMIT/MGH

POC Comparison: *Performance Gap*

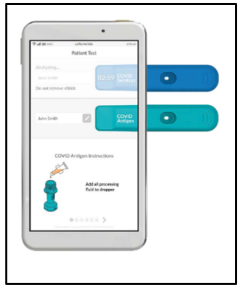
POC RTPCR

Visby Medical

Mesa BioTech

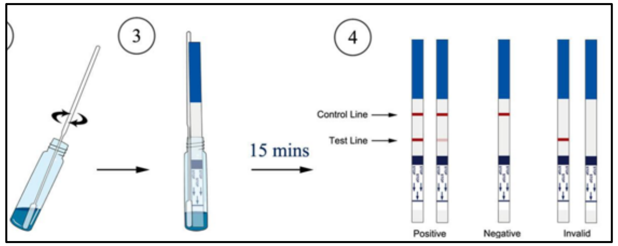
POC An (LFA/reader)

Quidel Sophia



Ellume

POC An (LFA/visual)



Maxim

	POC RTPCR	POC An (LFA/reader)		POC An (LFA/visual)
Cost	$$$	$$	$$	$
Speed	~30 min	<15 min	→	→
Sens/Spec (EUA)	>90/95	>90/95	→	→
LOD	~10^3 Cp/mL	~10^6 Cp/mL	→	→

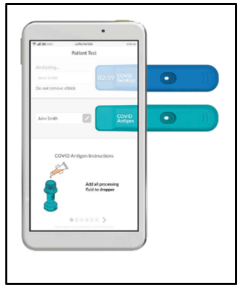
POC Comparison: *Performance Gap*

	POC RTPCR	POC An (LFA/reader)		POC An (LFA/visual)
	Visby Medical, Mesa BioTech	Quidel Sophia	Ellume	Maxim
Cost	$$	$	$	0.5 $
Speed	~30 min	<15 min		
Sens/Spec (EUA)	>90/95	>90/95		
LOD	~10^3 Cp/mL	~10^6 Cp/mL		

Visby Medical

Mesa BioTech


Quidel Sophia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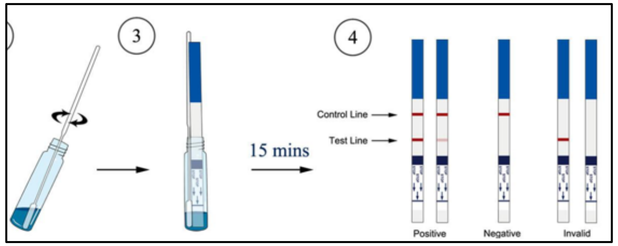


Maxim

Tech to Bridge the Gap

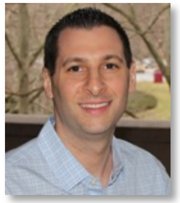
1) Separation/concentration
2) µ-Fluidics
3) Chemistries, e.g. CRISPR
4) Labels, Reporters
5) Readout/Sensing
6) ? ("Background" reduction)

RADx Digital Health Networks: *Integration*

RADx POC Test

Wearables

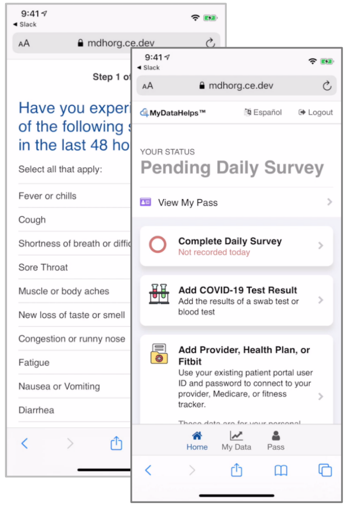
Digital Contact Tracing

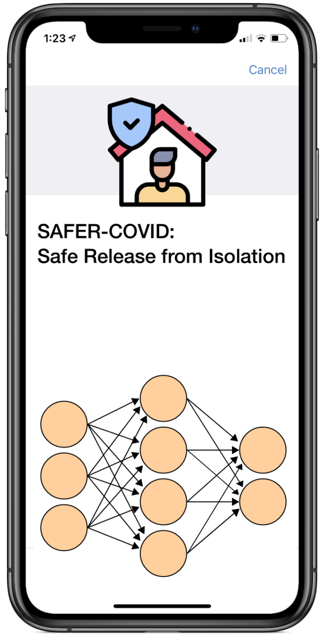


Andrew Weitz
NIBIB

Jason Levine
NCI

Symptom Surveys





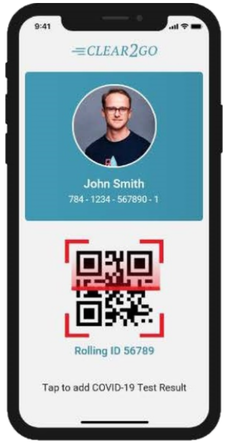
EHR & Claims

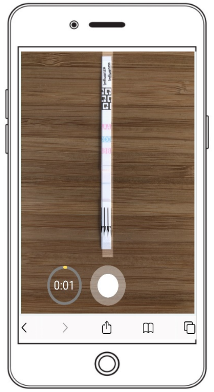
SYNC FOR SCIENCE

HL7 FHIR

Blue Button Download My Data

Proof of Health Status





Cell Phone Reader

e.g. OpenRDT (Audere)

GATES foundation

RADx Tech/ATP Summary

RADx Tech/ATP:

Accelerating innovation, Multiple platforms, Millions tests/day

Link NVBL to RADx network?

Implementation Challenge:

- Standard Medical Diagnostics: *accurately detect/diagnose disease in individuals*
- **COVID Paradox:** ***rapidly assess +/- of disease in asymptomatic populations:*** **Home?**
- Barriers: *Economic, cultural, regulatory*

Technical Challenges:

- Match tests w/biology of infection; needs of user communities *(what/when/how often?)*
- Bridge Tech performance gap: *improve performance in low prevalence settings*
- Integrate: *tests, models, interventions, Apps/data, for personal and PH management*