Rapid Acceleration of Diagnostics: RADx Tech/ATP

Advisory Council to the Director, December 10, 2020

Bruce J. Tromberg, Ph.D.
Director
National Institute of Biomedical Imaging and Bioengineering
NIH Office of the Director

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

RADx Tech – $500M
Highly competitive, rapid three-phase challenge to identify the best rapid or 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

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

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

$307 M Partnership with BARDA
Point-of-Care Technologies Research Network (POCTRN)

**NIBIB National Network:** 5-6 years for new POC technologies
Established 2007, Expanded 2020: >1,000 RADx experts & contributors

https://www.poctrn.org

**Project Tech:**
1) Review
2) Funding
3) Expertise
4) Testing

**Validation Core**
~50 projects complete, >2,000 participants

**Clinical Studies Core**
Standard Trial Design, Digital Health Platform, Single IRB, Center Network

**Deployment Core**
Supply chain, Manufacturing, User Community, End to end solutions
NIBIB National Network: **5-6 years for new POC technologies**

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

[https://www.poctrn.org](https://www.poctrn.org)

**Coordinating Center**

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

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

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

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

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

**Supporting Centers**

- **Duke/UNC CDCC**
- **RADx UP**

**Core Components**

- **Validation Core**
- **Clinical Studies Core**
- **Deployment Core**
RADx Tech/ATP Innovation Funnel

NATIONAL CALL FOR INNOVATIVE TECHNOLOGIES

- Rolling submission open April 29

Applications Started

~3000

Projects in each Phase

- June ACD: 434
- PHASE 0: "Shark Tank" Like Rapid Selection Process: 716
- PHASE 1: Validation and Risk Review: 136
- PHASE 2: Clinical Tests, Regulatory Approval, and Scaling Up: 47
- END OF SUMMER/FALL 2020: 22 (Tech + ATP)

DEPLOY MILLIONS of tests per week

Validation, Clinical Testing, Regulatory, Manufacturing, Distribution

~$480M
### Manufacturing Expansion Summary

- **Type:** 17 Nucleic Acid, 5 Viral Antigen
- **Setting:** 8 POC, 3 “between”, 11 Lab
- **Regulatory:** EUA → 8 lab, 3 POC
- **Impact:** ~1.5 M tests/day (Jan)

- **Pipeline:** 21 POC (9 NAT, 11 An, 1 VOC)
- **Impact:** >1 M LFA tests/day (Q1 2021)

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### Table: Projects in each Phase

<table>
<thead>
<tr>
<th>NATIONAL CALL FOR INNOVATIVE TECHNOLOGIES</th>
<th>PHASE 0: “Shark Tank” Like Rapid Selection Process</th>
<th>PHASE 1: Validation and Risk Review</th>
<th>PHASE 2: Clinical Tests, Regulatory Approval, and Scaling Up</th>
<th>END OF SUMMER/FALL 2020</th>
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</thead>
<tbody>
<tr>
<td>~3000 Applications Started</td>
<td>787</td>
<td>156</td>
<td>47</td>
<td>5-6 Months</td>
</tr>
<tr>
<td>Projects in each Phase</td>
<td></td>
<td></td>
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<tr>
<td>707</td>
<td>136</td>
<td>47</td>
<td></td>
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</table>

- **Rolling submission open April 29**
- **5-6 Months**
- **>6 M tests/day by end of year**
- **~$480M**

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**RADx Tech/ATP Innovation Funnel**

**DEPLOY MILLIONS**

of tests per week

**Validation, Clinical Testing, Regulatory, Manufacturing, Distribution**

*NIH*

**National Institute of Biomedical Imaging and Bioengineering**
Innovation
1) Separation/concentration
2) μ-Fluidics
3) Chemistries, e.g. CRISPR, NGS
4) Labels, Reporters
5) Readout Tech
6) Miniaturization
7) Automation

**22 Manufacturing Expansion**

November
~590,000 tests/day sold;
~890,000 tests/day capacity

https://www.nibib.nih.gov/covid-19/radx-tech-program/radx-tech-phase2-awards
<table>
<thead>
<tr>
<th>Company</th>
<th>Test Type</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesa BioTech</td>
<td>Nucleic Acid: RTPCR</td>
<td>POC</td>
</tr>
<tr>
<td>MicroGEM International</td>
<td>Nucleic Acid: RTPCR</td>
<td>POC</td>
</tr>
<tr>
<td>Mesa Biotech, Inc.</td>
<td>Nucleic Acid: RTPCR</td>
<td>POC</td>
</tr>
<tr>
<td>Talis Biomedical Corp.</td>
<td>Nucleic Acid: Isothermal PCR</td>
<td>POC</td>
</tr>
<tr>
<td>MatMaCorp</td>
<td>Nucleic Acid: RTPCR</td>
<td>Lab/POC</td>
</tr>
<tr>
<td>Ubiquitome</td>
<td>Nucleic Acid: RTPCR</td>
<td>Lab/POC</td>
</tr>
<tr>
<td>Maxim Biomedical Inc</td>
<td>Antigen: LFA dipstick</td>
<td>POC/home</td>
</tr>
<tr>
<td>Luminostics, Inc.</td>
<td>Antigen: LFA</td>
<td>POC/home</td>
</tr>
<tr>
<td>Ellume USA LLC</td>
<td>Antigen: LFA</td>
<td>POC/home</td>
</tr>
<tr>
<td>Quidel Corp.</td>
<td>Antigen: LFA</td>
<td>POC/home</td>
</tr>
<tr>
<td>Quanterix</td>
<td>Antigen/microbeads</td>
<td>Lab</td>
</tr>
<tr>
<td>Mammoth Biosciences</td>
<td>Nucleic Acid: CRISPR</td>
<td>Lab</td>
</tr>
<tr>
<td>Flambeau Diagnostics</td>
<td>Nucleic Acid: Isothermal PCR</td>
<td>Mobile Lab</td>
</tr>
<tr>
<td>Ceres Nanosciences Inc</td>
<td>Nucleic Acid: Extraction</td>
<td>Lab</td>
</tr>
<tr>
<td>Fluidigm</td>
<td>Nucleic Acid: RTPCR</td>
<td>Lab</td>
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<td>Broad Institute</td>
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<tr>
<td>Illumina Inc</td>
<td>Nucleic Acid: NGS</td>
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<td>Helix OpCo, LLC</td>
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<td>Ginkgo Bioworks</td>
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<td>Sonic Healthcare USA</td>
<td>Nucleic Acid: RTPCR</td>
<td>Lab Network</td>
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<td>PathGroup</td>
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<td>Aegis Sciences</td>
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Leveraging NIH Proof of Concept (PoC) Network

~50 early-stage RADx-tech projects
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

RADx Test Validation Core (Emory-Gtech)

50 projects complete

Wilbur Lam    Greg Martin.   Oliver Brand

>2,000 participants
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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 BTI facility, Children’s Healthcare of Atlanta clinical pathology laboratories, and laboratories in 

OVERALL SUMMARY OF RESULTS ACROSS ACME POCT SITES

Prospective Clinical Results
DiaSorin RT-PCR

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Lack of Cross-Reactivity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC43 seasonal coronavirus</td>
<td>✓</td>
</tr>
<tr>
<td>MERS (heat inactivated)</td>
<td>✓</td>
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Sensitivity: 100%
Specificity: 100%

* PNNS, pooled negative nasal swab
**Challenge:** Compare NAT and Antigen Test Performance

**Viral Antigen Test**
Lateral Flow Assay (LFA)
LOD: TCID<sub>50</sub>/mL ~10<sup>3</sup>-10<sup>4</sup>/mL

**Nucleic Acid Test**
RTPCR (Isothermal PCR)
LOD: Cp/mL ~10<sup>2</sup>-10<sup>3</sup>/mL

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Understanding Screening/Surveillance Performance

Impact of LOD and Population Viral Load on Performance

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

- Wide range of viral loads in population
- Generally higher with time after onset
- Levels not correlated with infectiousness

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

**Impact of LOD and Population Viral Load on Performance**

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

- **LFA**
  - Typical LOD $\sim 10^6$ Copies/mL
  - Sensitivity $\sim 40\%$ vs. RTPCR for all (symptomatic + asymptomatic)

- **Vs.**
  - Sens/Spec $\sim 90/95\%$ for symptomatic population (EUA: $\sim 5$ days post-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
Understanding Screening/Surveillance Performance

Impact of LOD and Population Viral Load on Performance

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

NAT $\rightarrow$ Typical LOD $> \sim 10^2$ Copies/mL
Sensitivity $>\sim 90\%$ 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)

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

- 2 Technologies tested (>500 subjects)
- 3 in progress (Quidel, MicroGem, Quanterix) w/~1000 subjects
- Quidel Multisite study: *UMass, UIUC, JHU*
  - Longitudinal sequential Lateral Flow Assay (LFA) assessment (2 weeks)
  - RTPCR, saliva, + viral infectiousness assay
- LFA home testing in design phase
  - Self sampling, digital health platforms, break chain of transmission?
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

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.

www.poctrn.org
RADx webinars, tools
https://whentotest.org/

Anette Hosoi
MIT
Paul Tessier,
CIMIT/MGH

Nancy Gagliano, MD
RADx Deployment Core (CIMIT)

COVID-19 TESTING IMPACT CALCULATOR

START HERE

How many people are in your organization?

What percentage reliably wear masks?

Do you have a contact tracing program?

If you offer unmasked group activities such as dining or meetings, how many people are in a group?

If your employees will be paid during testing, what is their average hourly wage?

If you are paying people to conduct testing, what is their average hourly wage?

COST CONSIDERATIONS

Estimated Testing Cost per Week

Total Number of People to be Tested each Day

(assumining testing 7 days per week)

If you are testing 5 days per week instead of 7, then multiply this # by 1.4 to obtain the Total Number of People to be Tested each Day (up to the maximum # of people within your organization). Do not test any individual more than once per day.

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

www.poctrn.org
RADx webinars, tools

https://whentotest.org/

Anette Hosoi
MIT
Paul Tessier,
CIMIT/MGH
Implementation Challenges:

- *Screening/Surveillance:* assess +/- of disease in asymptomatic populations
- *Create “at home” use path:* prescription, OTC
- *Economic, regulatory, reporting structures to support screening/surveillance*
Implementation Challenges:

- Screening/Surveillance: assess +/- of disease in asymptomatic populations
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Tech Development and Expansion:

- Millions accessible tests/day in 2021 (Q1/2) for home use (LFA); OTC and w/prescription
- Digital Health Platforms (Apps) for public health and personal guidance
- Accessible ”break through” tech bridging PCR-LFA performance gap
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• Screening/Surveillance: assess +/- of disease in asymptomatic populations
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RADx Clinical Studies for Guidance:
• Can sequential LFA tests provide equivalent info to PCR for “infectiousness”?
• Can frequent, inexpensive LFA tests at home break chain of transmission?