

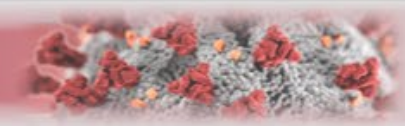


Rapid Acceleration of Diagnostics (RADx)

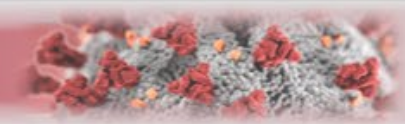
RADx Tech Technology Portfolio and Domain Analysis

How Innovation in the Development of
Testing Systems Helps Meet Diverse Needs

10/20/2020



- To describe *some* of the science and technology within RADx Tech
 - What kinds of testing methods are being developed for SARS-CoV-2?
 - How can innovation address the needs of the U.S. population **Rapidly**?
- To suggest the pathways for innovation in SARS-CoV-2 testing
 - How can various inventions help us **Accelerate** diagnostics & screening?
 - What kind of team does it take to be successful in this effort?
- To illustrate the technology and their usefulness in planning **Diagnostics**
 - How can we use visualization tools to understand the methods in RADx Tech?
 - What are the available products in relation to what's coming down the pike?



Am I infected ?



NP Swab

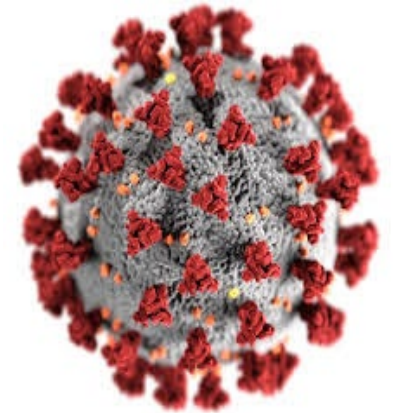
MT Swab



AN Swab

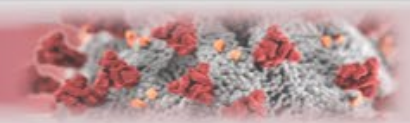


Saliva



**SARS-
CoV-2**

Viral Target Molecules



Spike Glycoprotein (S)

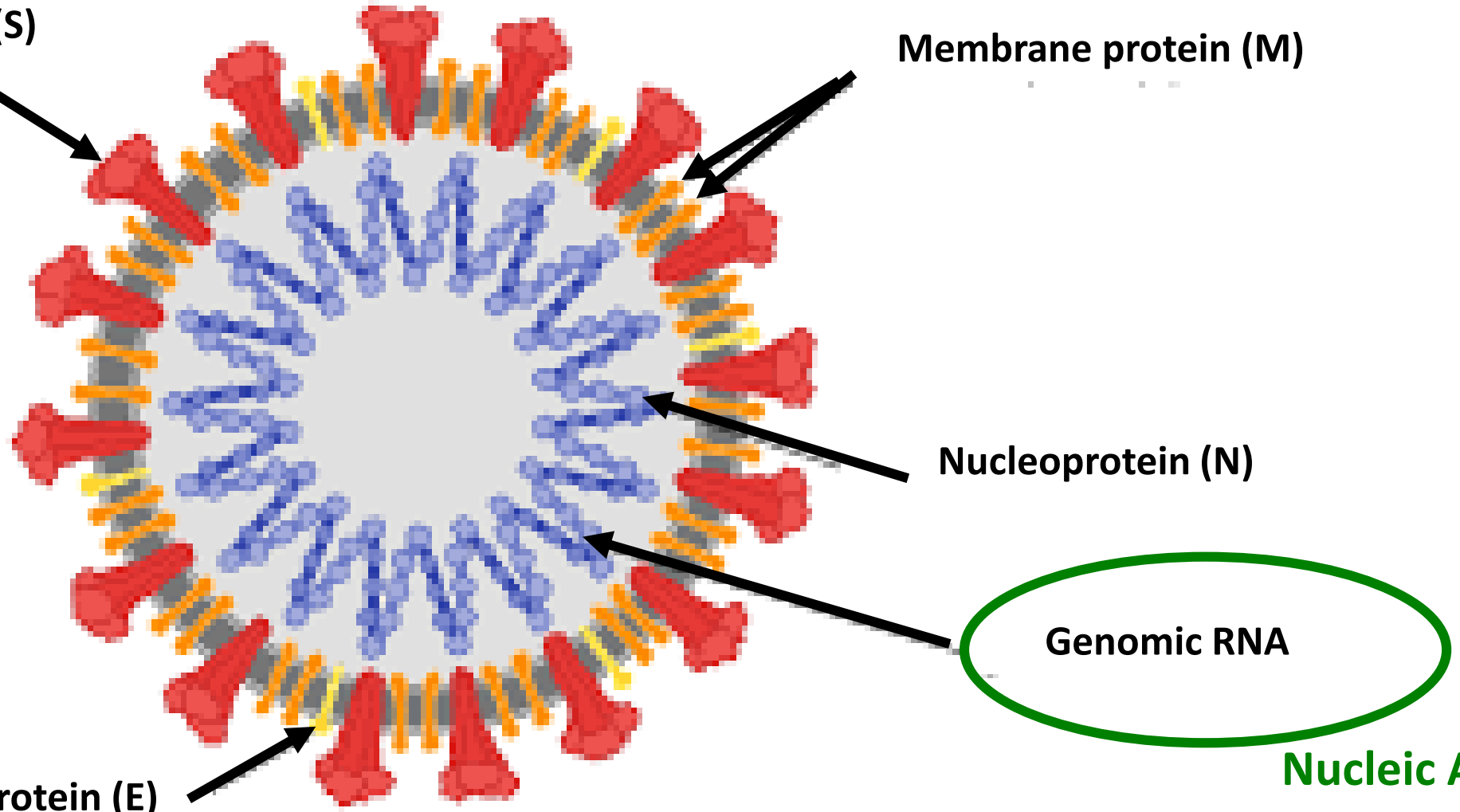
Membrane protein (M)

Nucleoprotein (N)

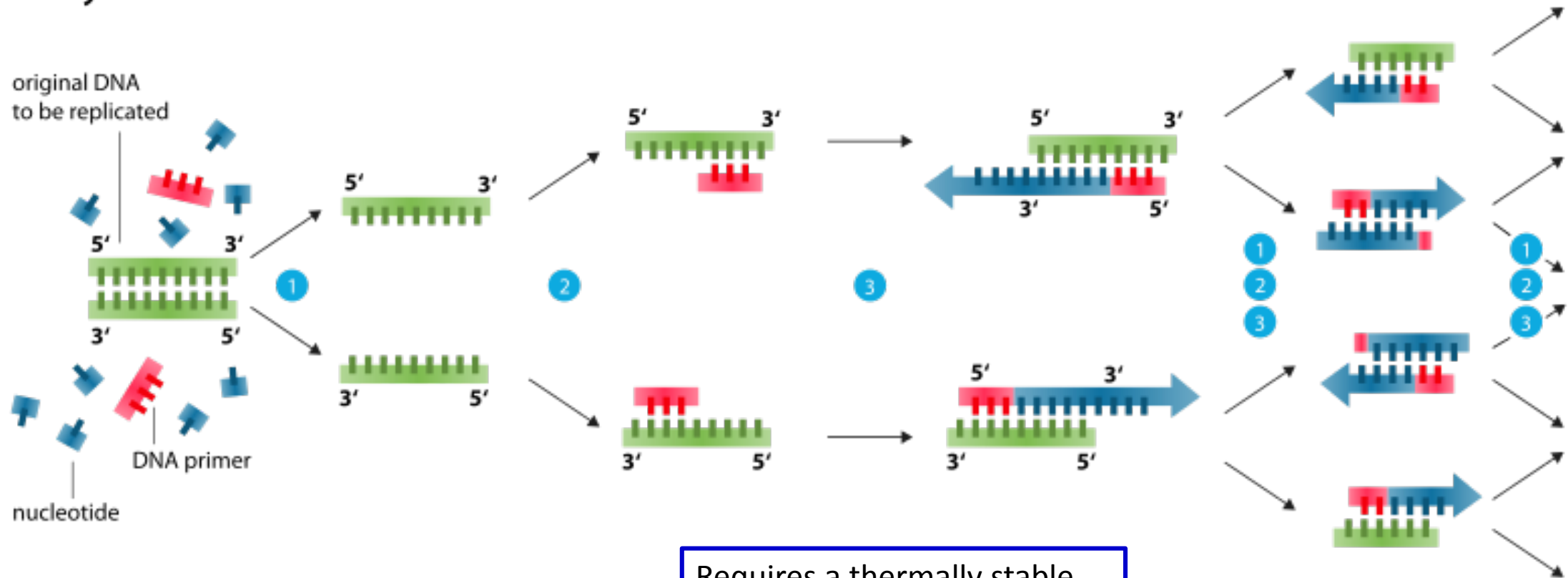
Genomic RNA

Nucleic Acid

Envelope small protein (E)



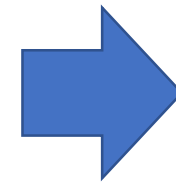
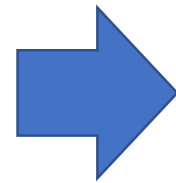
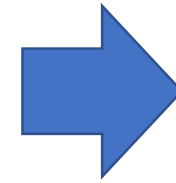
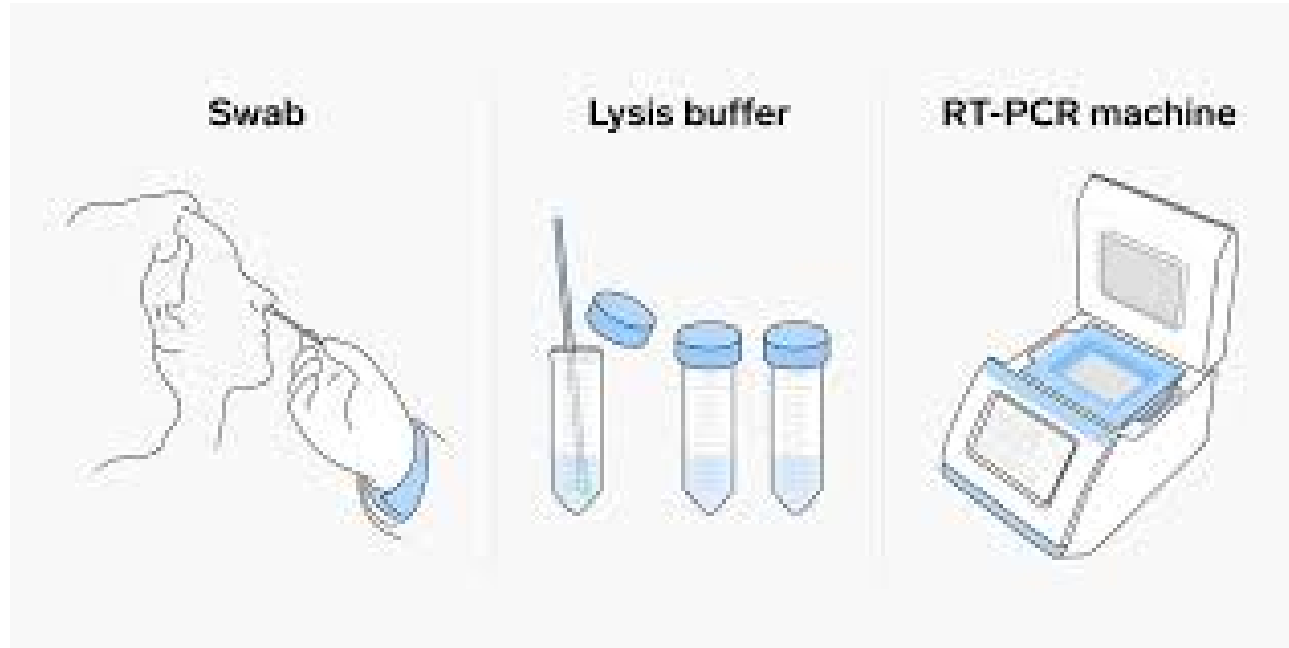
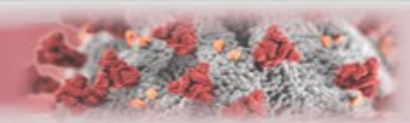
Polymerase chain reaction - PCR



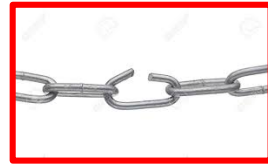
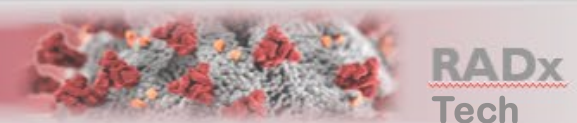
- 1 **Denaturation** at 94-96°C
- 2 **Annealing** at ~68°C
- 3 **Elongation** at ca. 72 °C

Requires a thermally stable DNA polymerase (e.g. Taq) and specific primers & dNTPs, all critical to the supply chain.

RT-PCR has been the Standard

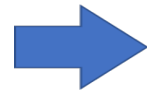


RT-PCR Nucleic Acid Testing



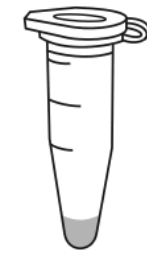
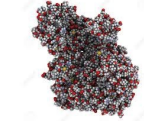
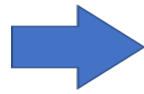
Sample (Lysed)

Purify RNA



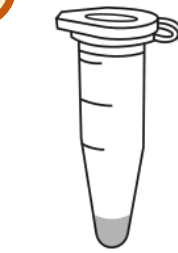
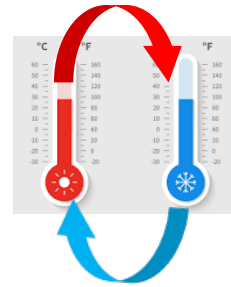
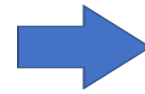
Viral RNA

(RT) Reverse transcribe



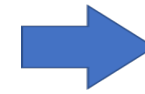
cDNA

Amplify $\times 2^{40}$ (PCR)



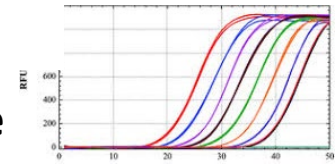
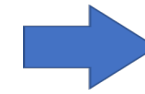
DNA Amplicons

Label Product



Measure Fluorescence

Calculate



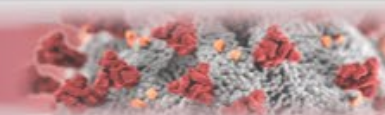
REPORT



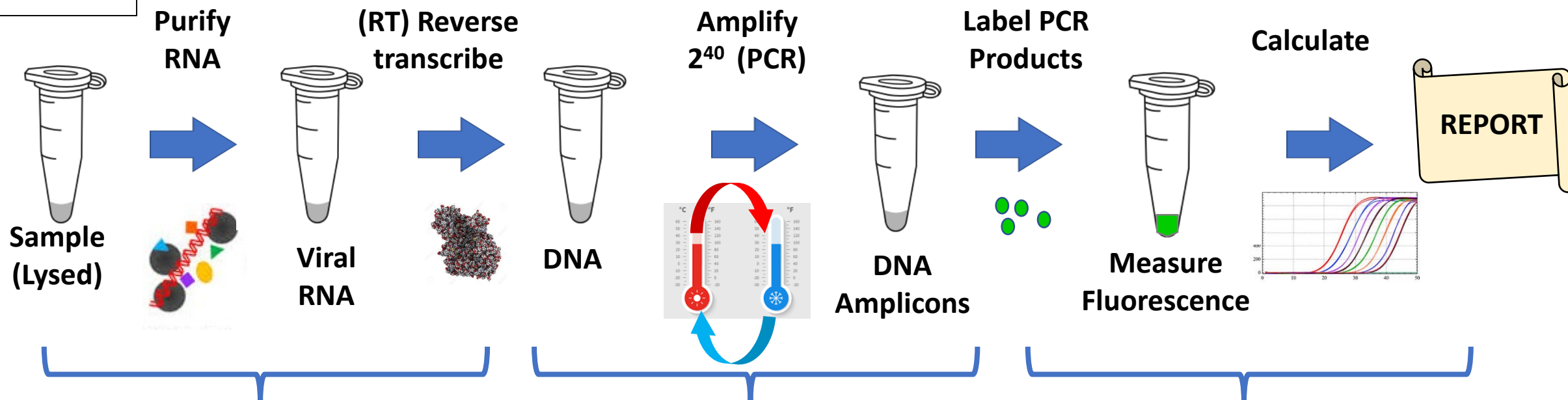
Patient, Physician, Public Health Dept., Local Regulations



Innovations for Nucleic Acid Testing



RT-PCR

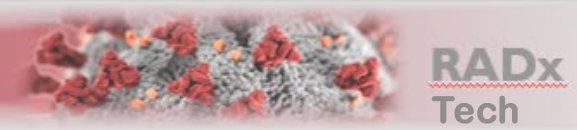


- Novel sample prep
- Extraction-free reaction
- Direct amplification
- CRISPR methods

- Rapid thermocycling
- Microfluidic cartridges
- Isothermal amplification
 - LAMP
 - Rolling Circle
 - Recomb. polymerase

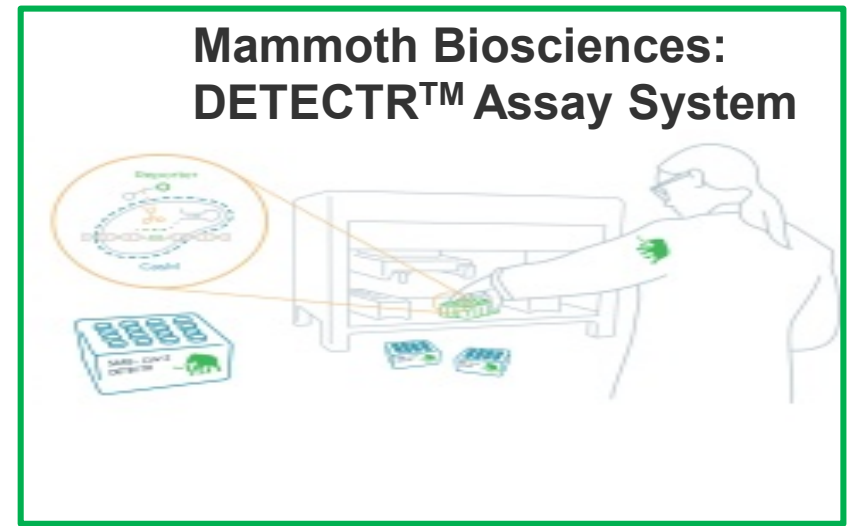
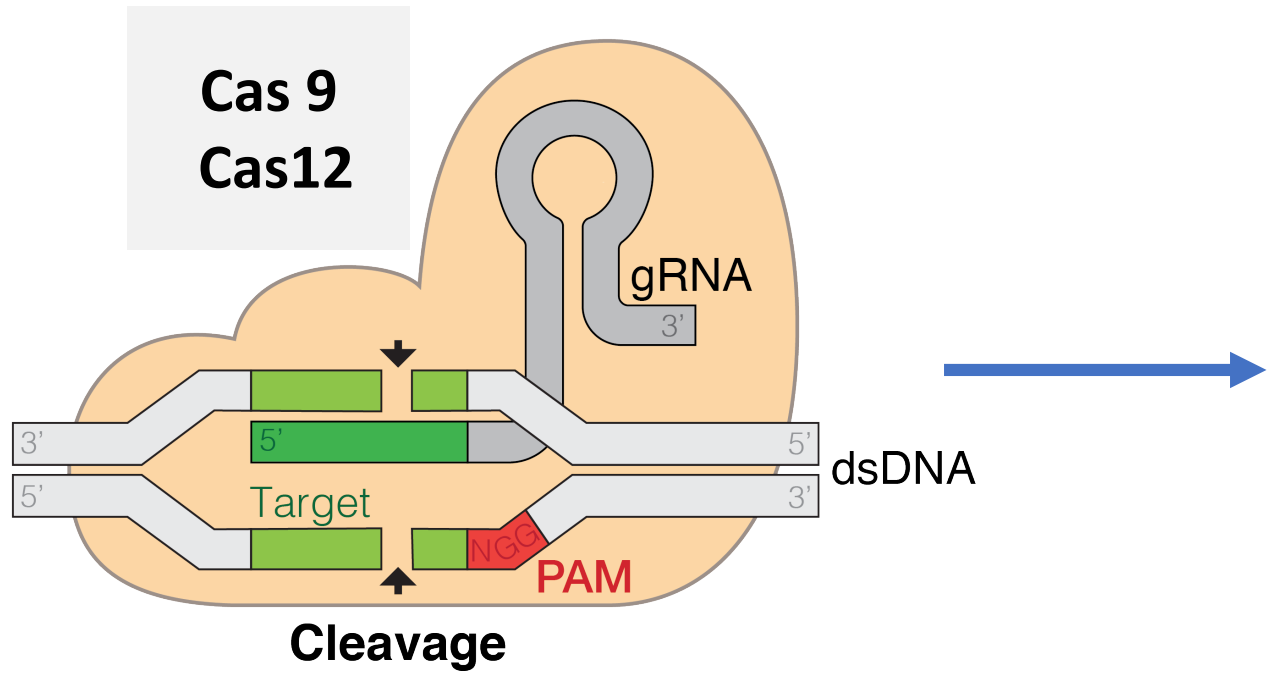
- Real Time qPCR
- Automation
- Cloud reporting
- Mobility
- Portability

Improvements: CRISPR



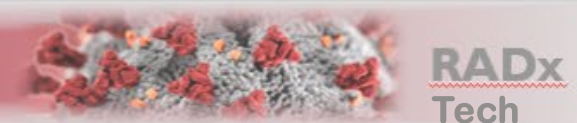
- Novel sample prep
- Extraction-free reaction
- Direct amplification
- **CRISPR methods**

Clustered,
Regularly
Interspaced,
Short
Palindromic
Repeats

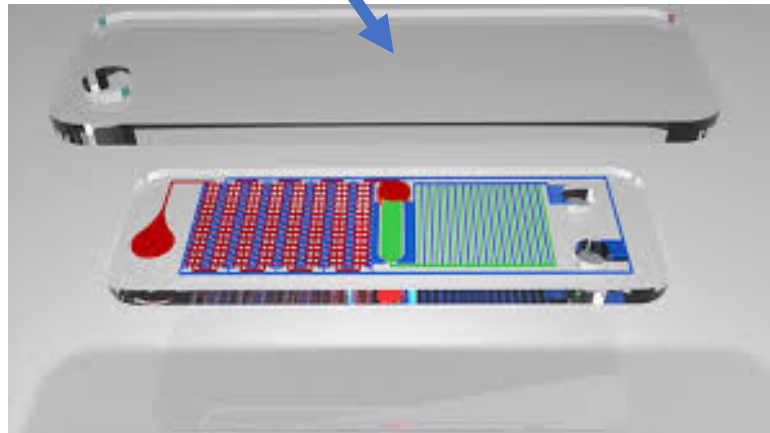


CRISPR-associated (Cas) endonucleases and other Cas proteins are used to bind specific RNA molecules and then trigger a molecular signal for detection.

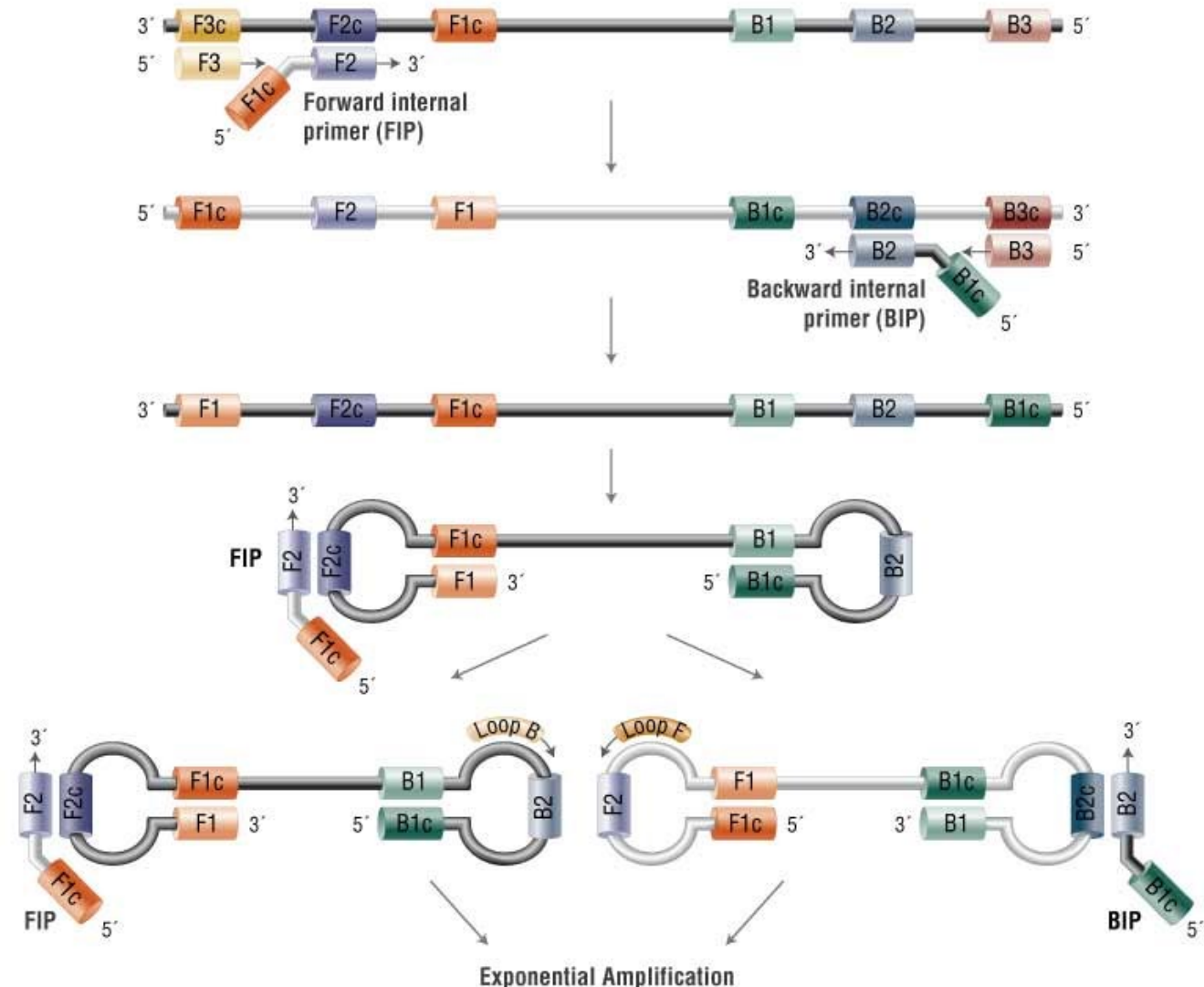
Improvements: Isothermal Amplification



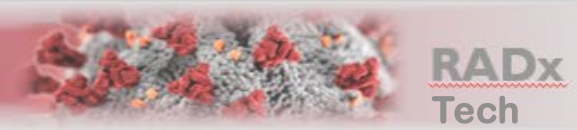
- Rapid thermocycling
- Isothermal amplification
 - LAMP
 - Rolling Circle
 - Recomb. polymerase
- Microfluidic cartridges



Loop-Mediated Isothermal Amplification (LAMP)



Improvements: Throughput & POC



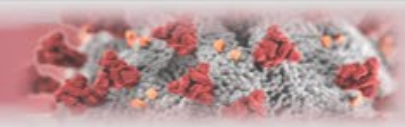
- Real Time qPCR
- Automated Liquid Handling
- Cloud reporting
- Mobility
- POCT / Portability



Oct. 13: Cue Health Monitoring System



- ### Intended RESULTS
- Ensure high-sensitivity nucleic acid tests are used
 - Reduce Turn-Around Time for sample handling & processing
 - Bring Testing to Point of Care
 - Get results to patients, physicians, and public health officials quickly & properly

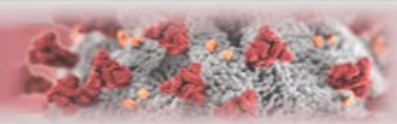


Innovation

- Microfluidic cartridges for POCT
- Automated liquid handling
- Cloud Reporting
- Mobility
- Isothermal methods

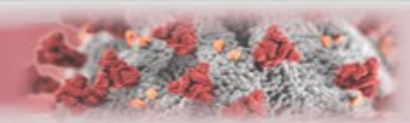
Obstacles

- Consumable supply, Cost and Manufacturing complexity
- Laboratory capital investment and Consumable supply chain
- Diverse device technologies, usability and compliance issues
- Deployment, training, logistics
- Licensing, Intellectual property



Viral Protein Antigen Assays

Viral Target Molecules



Spike Glycoprotein (S)

Protein

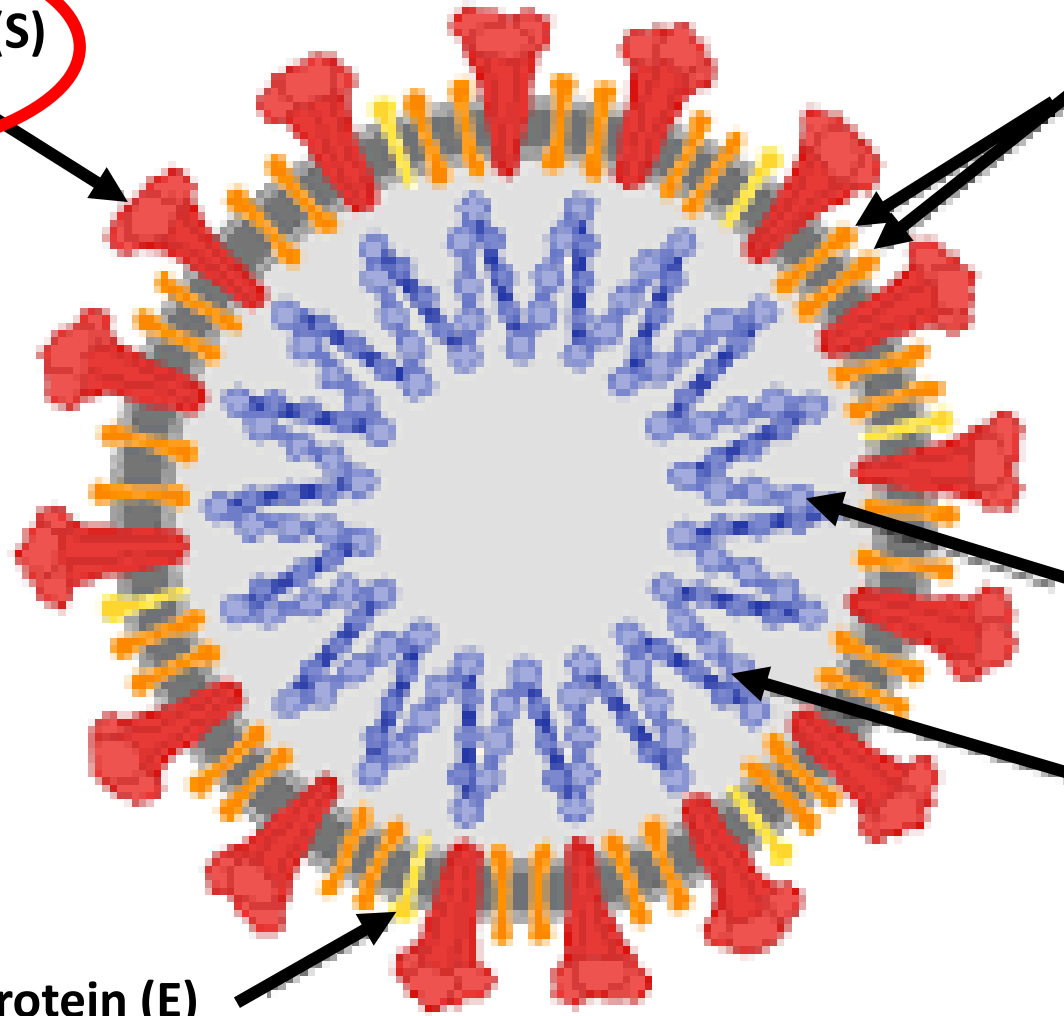
Membrane protein (M)

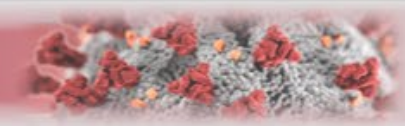
Protein

Nucleoprotein (N)

Genomic RNA

Envelope small protein (E)





- Spike Protein (S)

- Exposed on the viral surface
- Fewer copies per virus particle
- Conformational epitopes

- Nucleocapsid Protein (N)

- Viral lysis required
- More copies per virus particle
- Aggregates as multimers

- Immuno-Assays

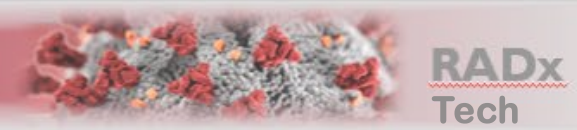
- Plate-based ELISAs
- Lateral Flow Assays
- Direct sensor chips
- Agglutination Assays

- Other Binding Assays

- Aptamer-based assays
- Imprinted polymers

- Mass Spectrometry

ImmunoAssays for Screening



Sandwich ELISA

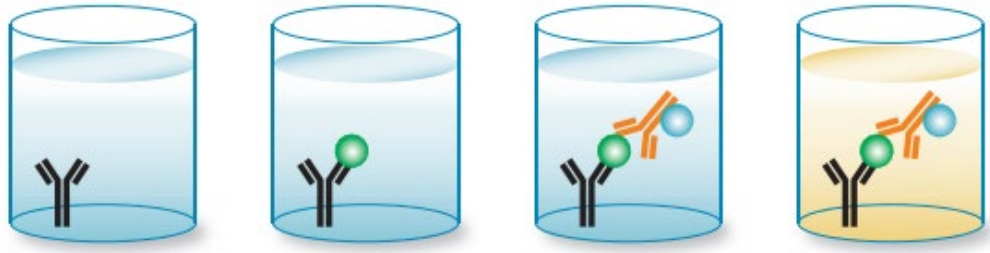
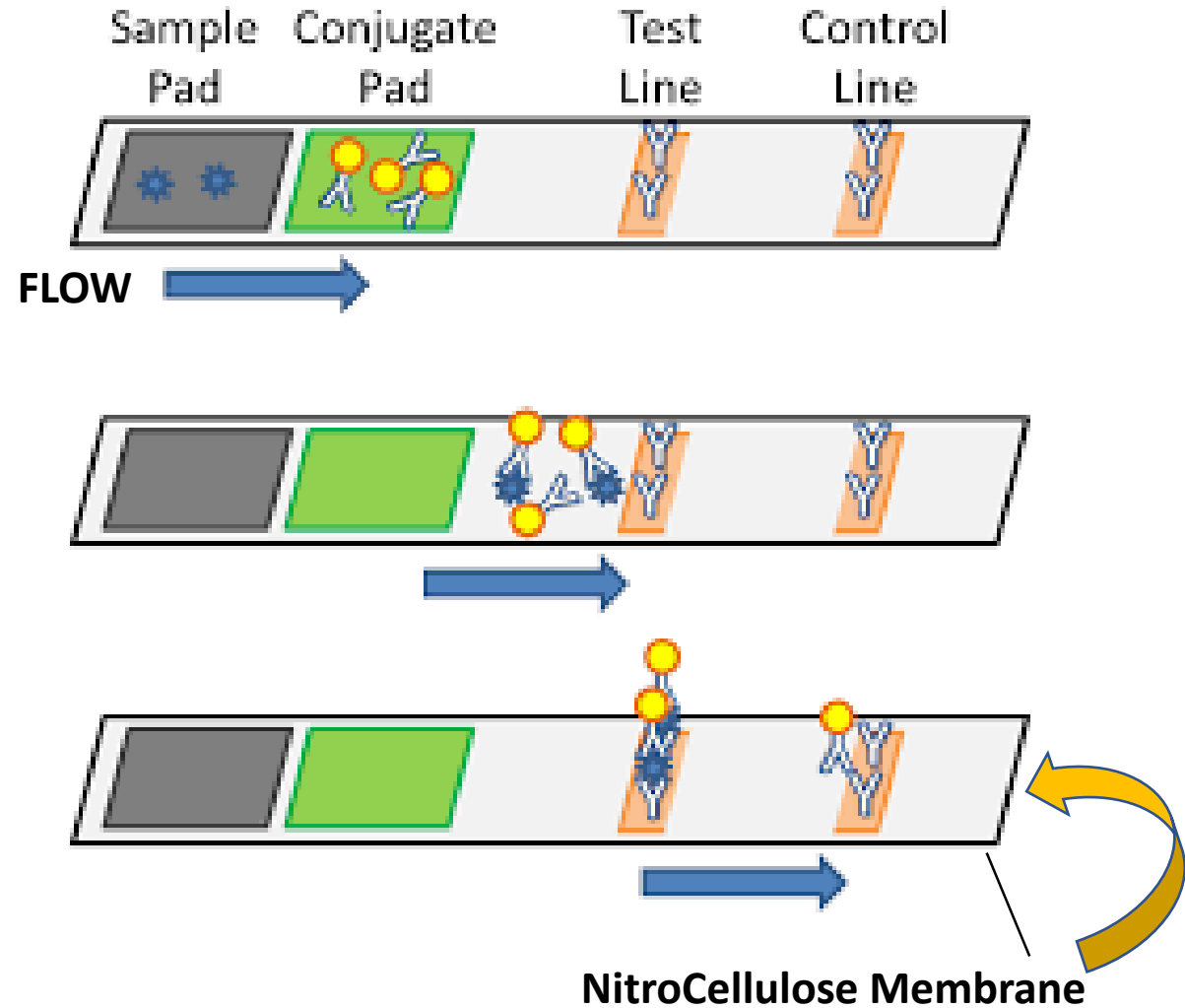


Plate Reader

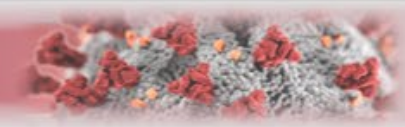


Lab Automation

Lateral Flow Assay



Challenges for Lateral Flow Assays



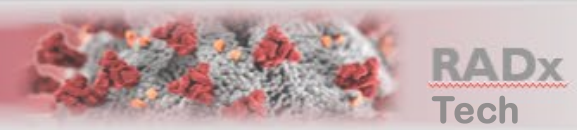
- Pairs of Antibodies
- Au Nanoparticle conjugates
- NitroCellulose Membranes
- Assembly /Manufacture
- Assessing outcome
- Reporting Methods
- Reflex Diagnostic testing



- Use of Aptamers or Nanobodies
- Use of Fluors and other dyes
- Supply Chain Issues
- Contract Manufacturing
- Visible detection or reader
- Cloud reporting
- Reflex to Nucleic Acid Diagnostic



Screening vs. Diagnostic Tests



Screening

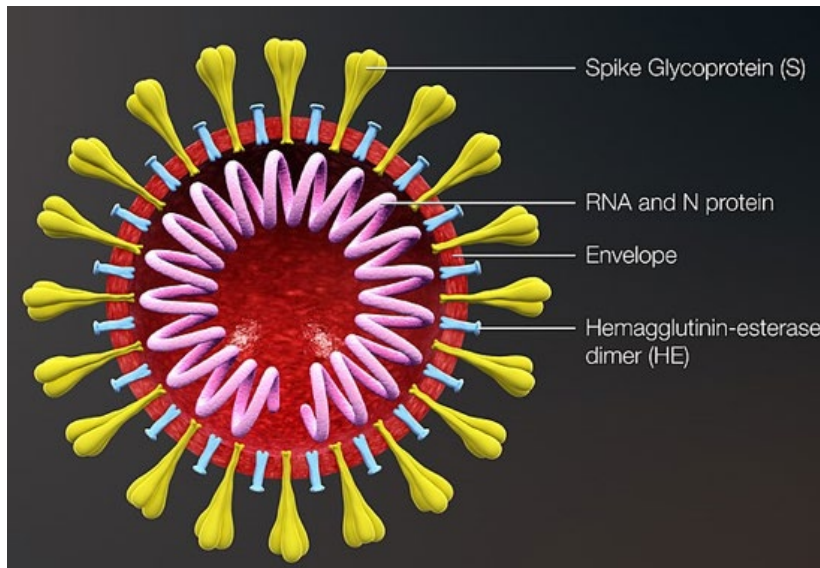
- Tests performed with goal of detecting pre-clinical infection or exposure to disease
 - Include antigen tests for presence of virus such as spike (S), nucleocapsid (N) proteins
 - Include antibody serology immunoglobulin assays for evidence of exposure (IgG/IgM)

Diagnostic

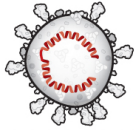
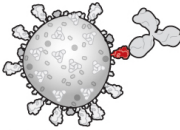

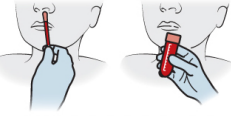
- Tests performed to identify the virus and confirmation of suspected infection
 - Detect viral RNA via producing copies of specific viral genes (PCR, isothermal, rolling circle tests)

Speed counts

Standard COVID-19 tests sacrifice speed and low cost for accurate diagnosis. Faster, cheaper screening tests could catch and isolate infected people more quickly.



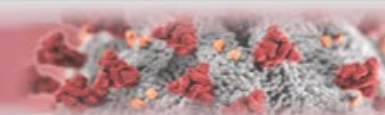
Cross section SARS-CoV-2 virus

	Diagnostic	Screening
Predominant type of test	RNA amplification 	Antigen testing 
Sample collection	Swab 	Swab or saliva 
Turnaround time	Days	Minutes
Cost	\$\$\$	\$
Accuracy	High	Moderate
Frequency	Single tests	Multiple tests every week



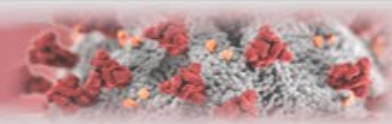
Mock-up lateral flow assay (LFA) IgG/IgM test
Source: NIH Director's Blog, 5/7/20

Other Specific Lab Testing Methods



- Next Generation DNA Sequencing
- Digital Droplet PCR Assays
- Digital Droplet Immunoassays
- Mass Spectra of Viral Proteins
- Imaging / AI

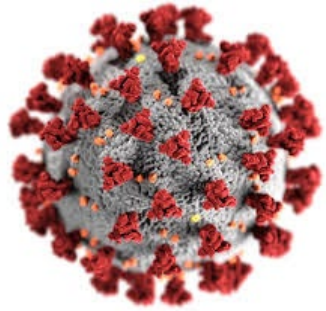




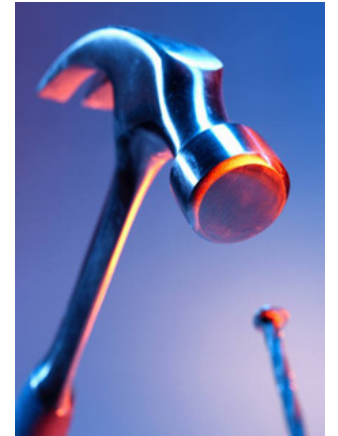
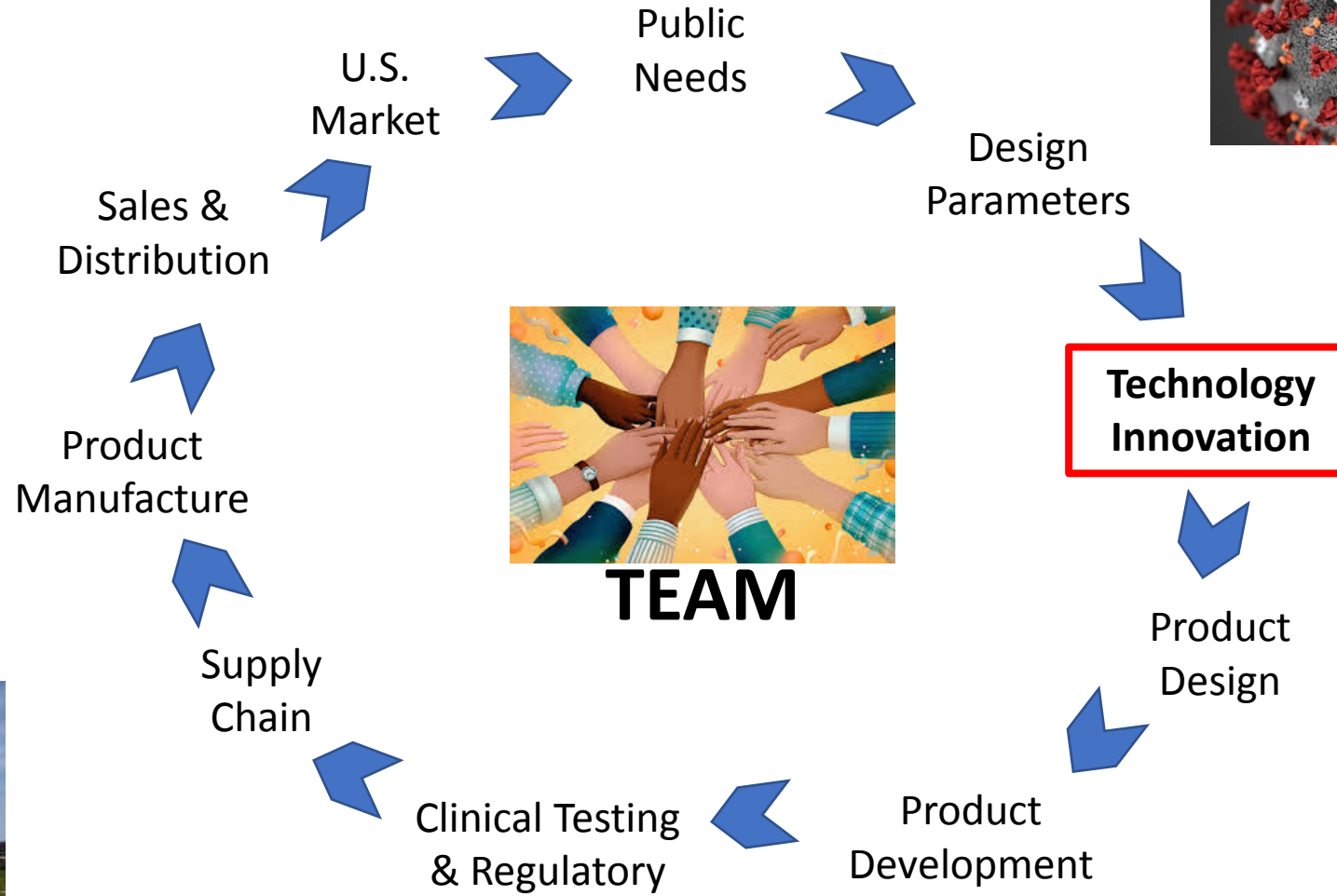
Building a Great Team

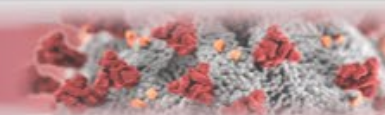
RADx Tech has seen that teams with diverse expertise are often required for successful product development. Collaboration and interaction are key qualities.

Innovation Challenges



SARS-CoV-2



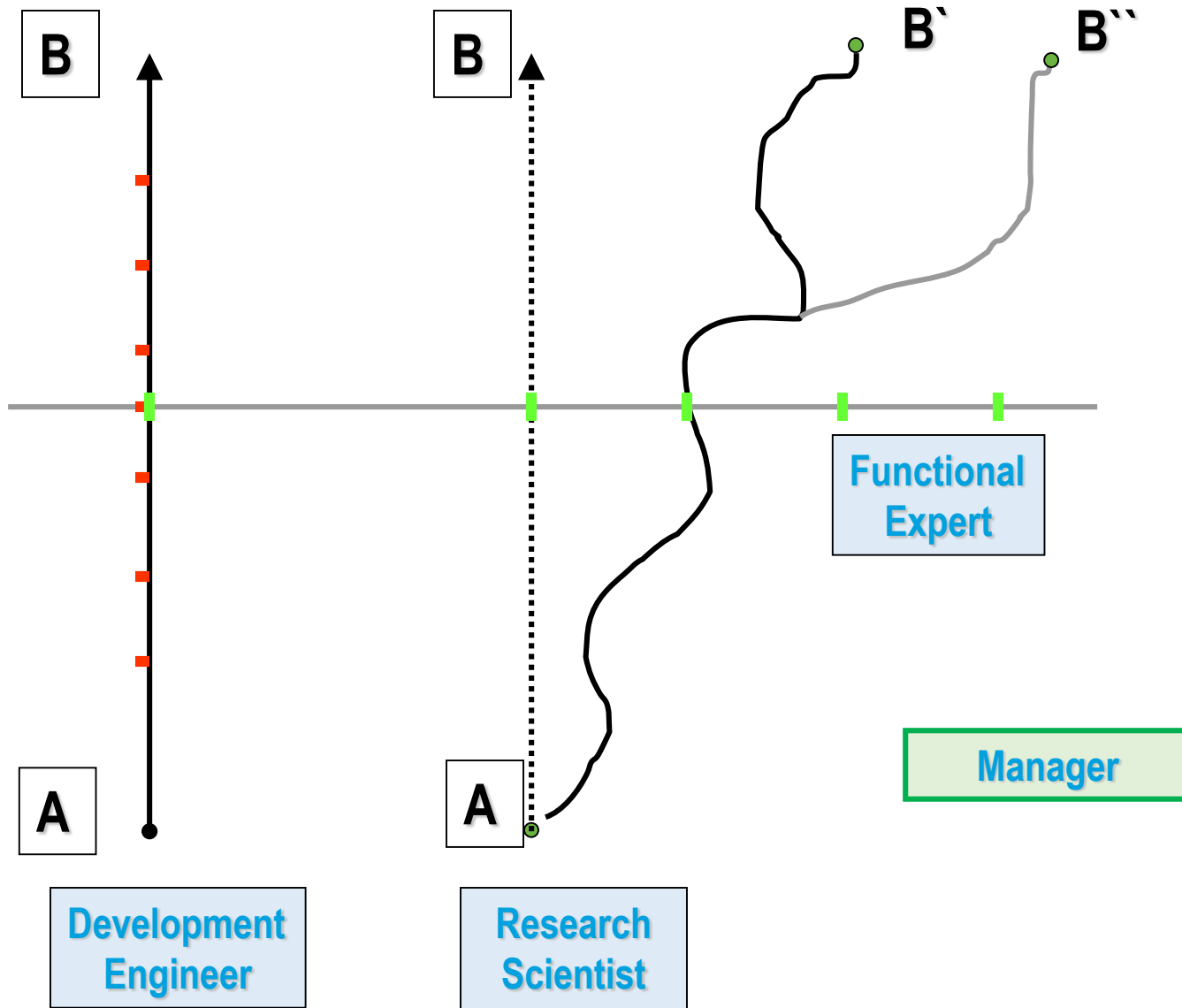
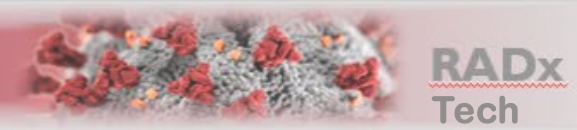


People Who Populate R & D

- **Scientists** new paths to knowledge
- **Engineers** design and build products
- **Experts** excellence in specific functions



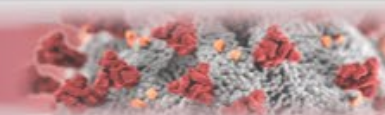
Different Approaches to a Project



What Makes a Great Team?

- ▶ Common Goal
 - The Lifeboat Drill
- ▶ Diversity
 - Scientists, Engineers, Functional Experts *and* Managers
- ▶ Communication
 - Formal and informal discussions
- ▶ Respect
 - Mutual acceptance of roles
- ▶ Stress
 - Performance improvements

CIMIT & Exaptive Collaborate



MASSACHUSETTS
GENERAL HOSPITAL

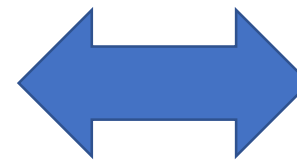
CIMIT: Center for
Integration of Medicine
& Innovative Technology



exaptive

A proof-of-concept experiment was conducted using the RADx Tech data with Exaptive's Cognitive City® platform to mine the data securely to help us understand the scope, nature, and strengths of the portfolio plus weaknesses to be addressed.

<https://www.massgeneral.org/research/cimit>



RADx Tech

Exaptive was founded in 2011 by Dave King, based on the idea that innovation doesn't have to wait for serendipity; innovation can be facilitated. Bringing collaborators with a mix of shared and unique perspectives together is a formula for exaptation. www.exaptive.com

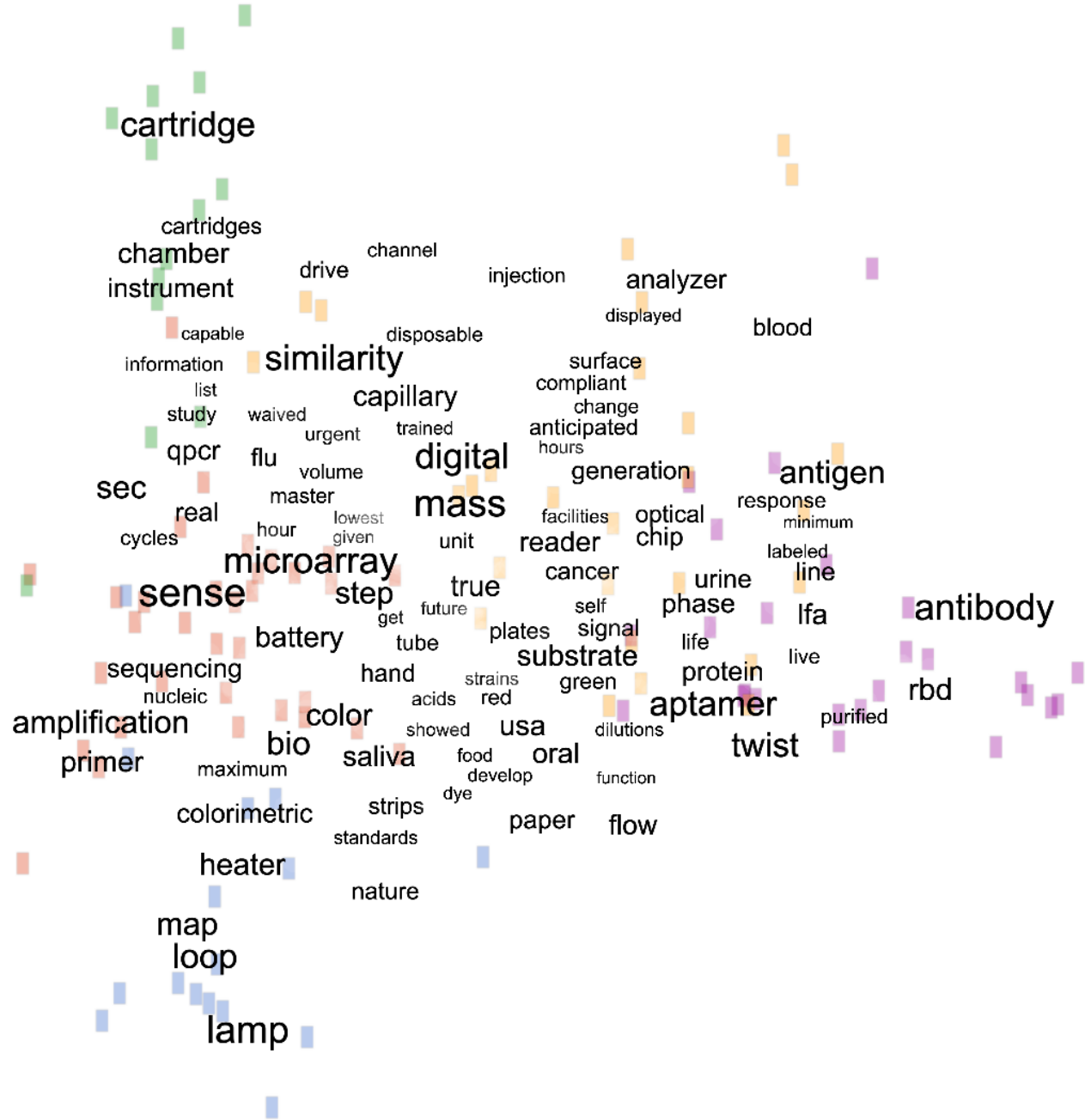
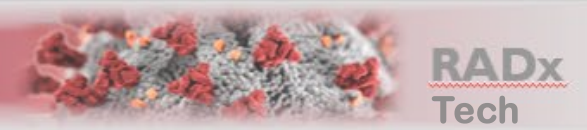
Cognitive City®

DISCOVER . CONNECT . TRANSFORM

Marshall Collins
& the RADx Team

Dave King & the
Exaptive Team

Termscape: CIMIT-Exaptive Collaboration



Project “Termscape”
 Similar projects are closer together,
 clustered by common terminology

Cluster 1

lamp saliva heater poc reaction

Cluster 2

kit amplification app plate saliva

Cluster 3

analyzer digital protein sensor antigen

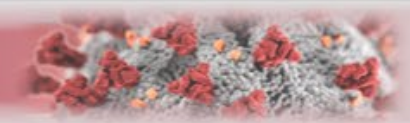
Cluster 4

cartridge instrument cartridges answer chamber

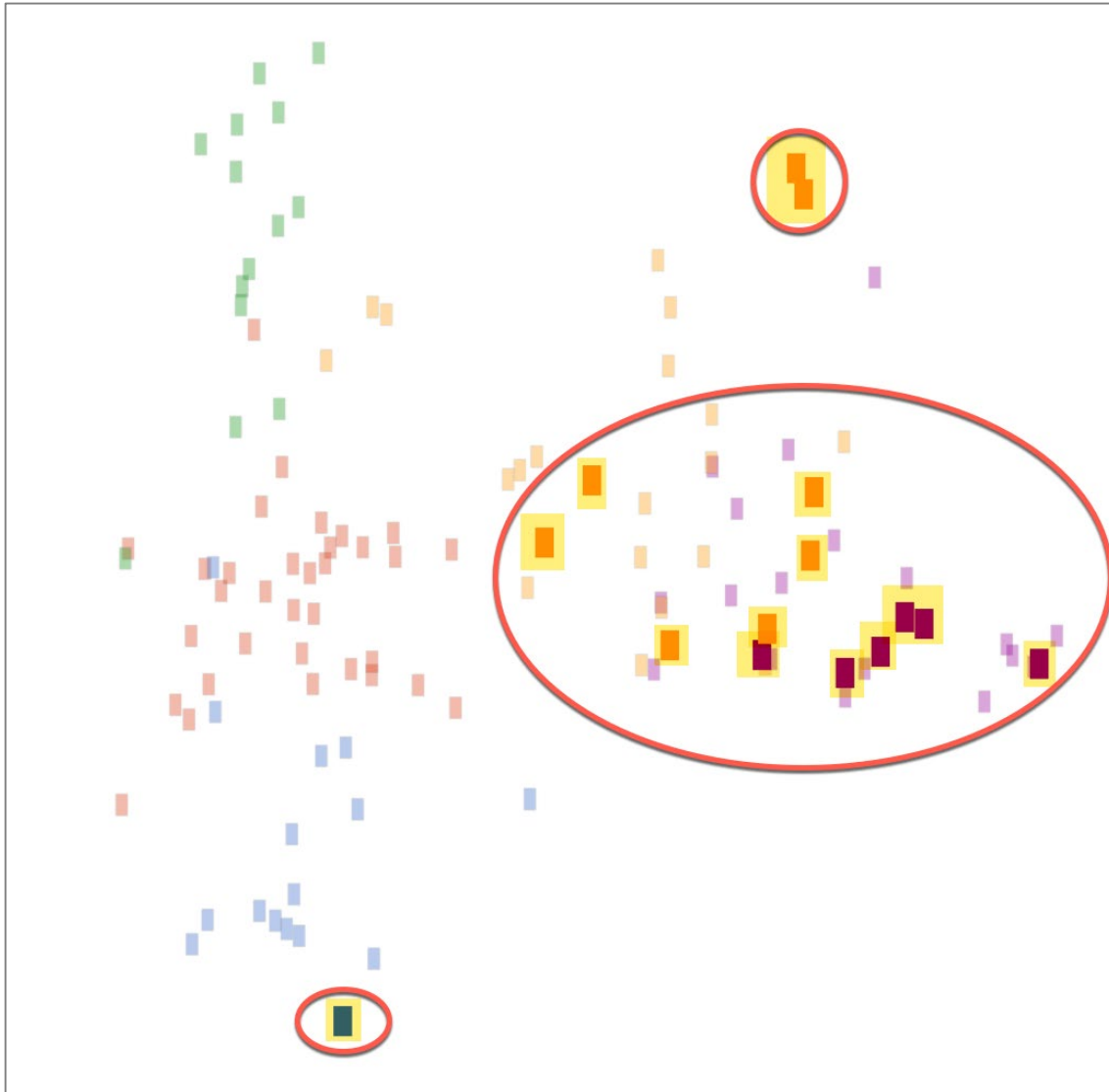
Cluster 5

antigen antibodies antibody aptamer lateral

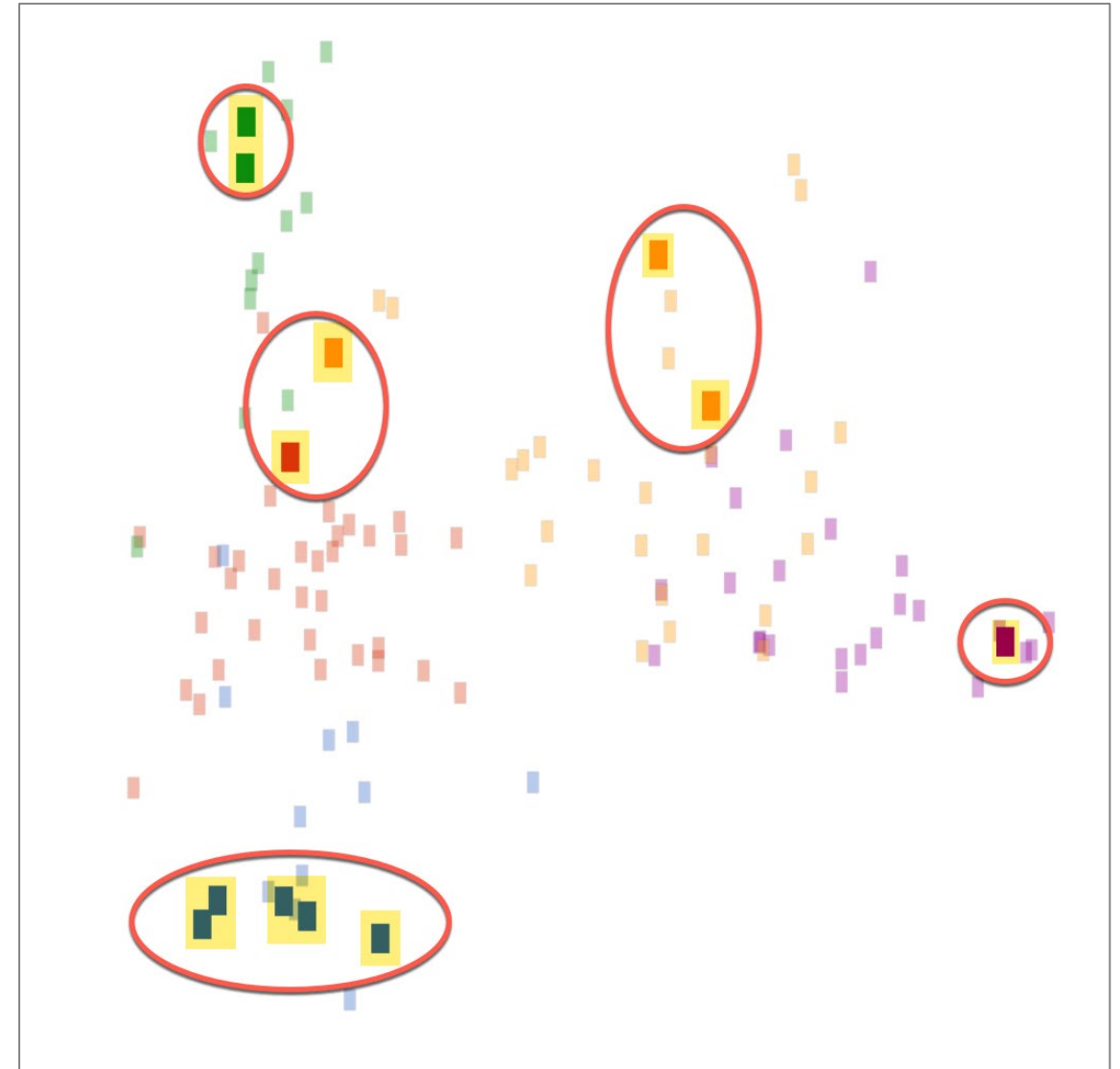
How Different Technologies Cluster



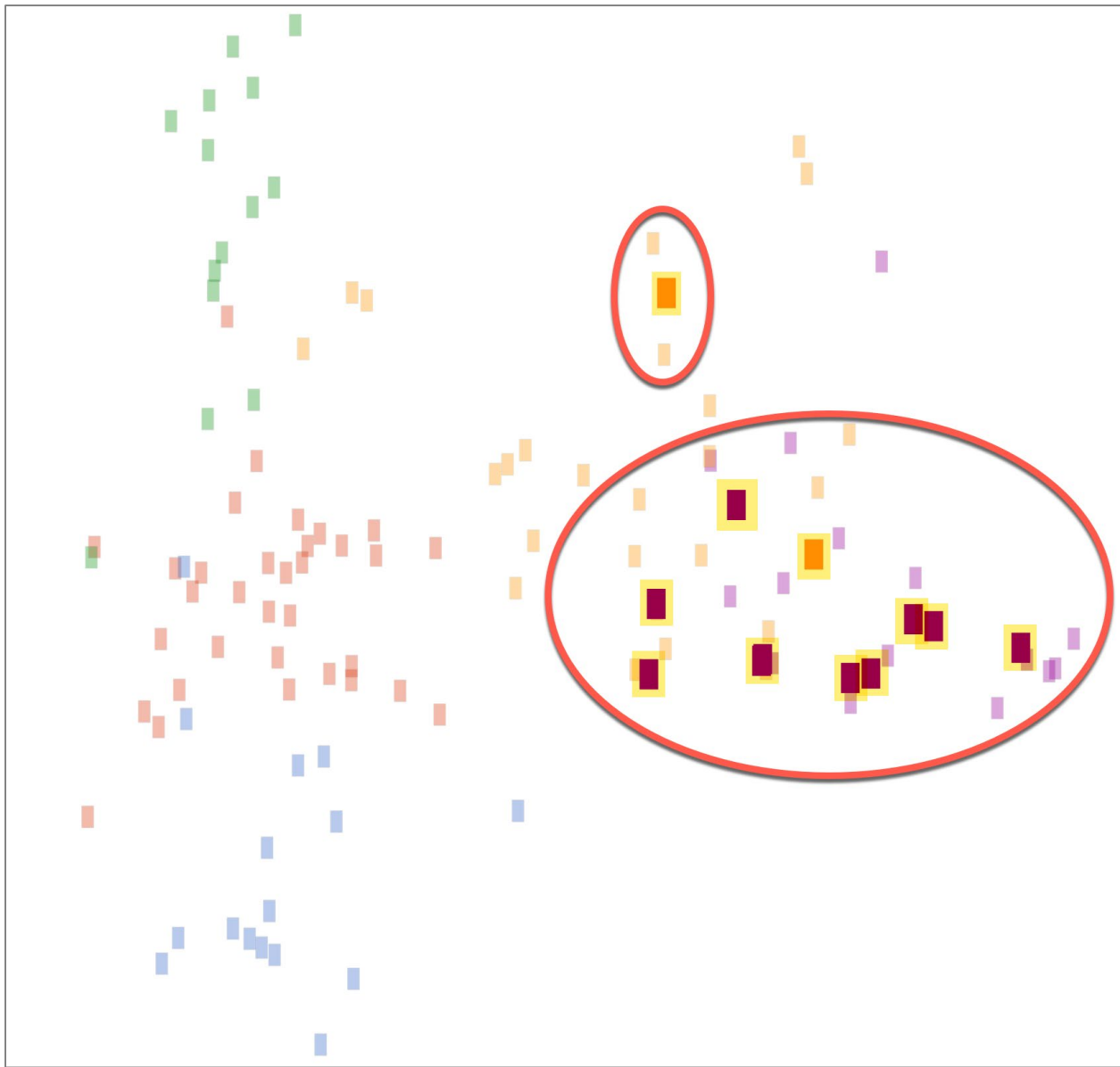
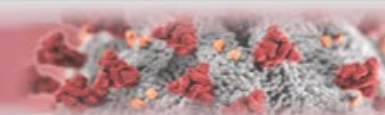
LFA Projects



CRISPR Projects



Supply Chain Challenge: Nitrocellulose



- Projects using NC membranes
- Nearby projects not using NC

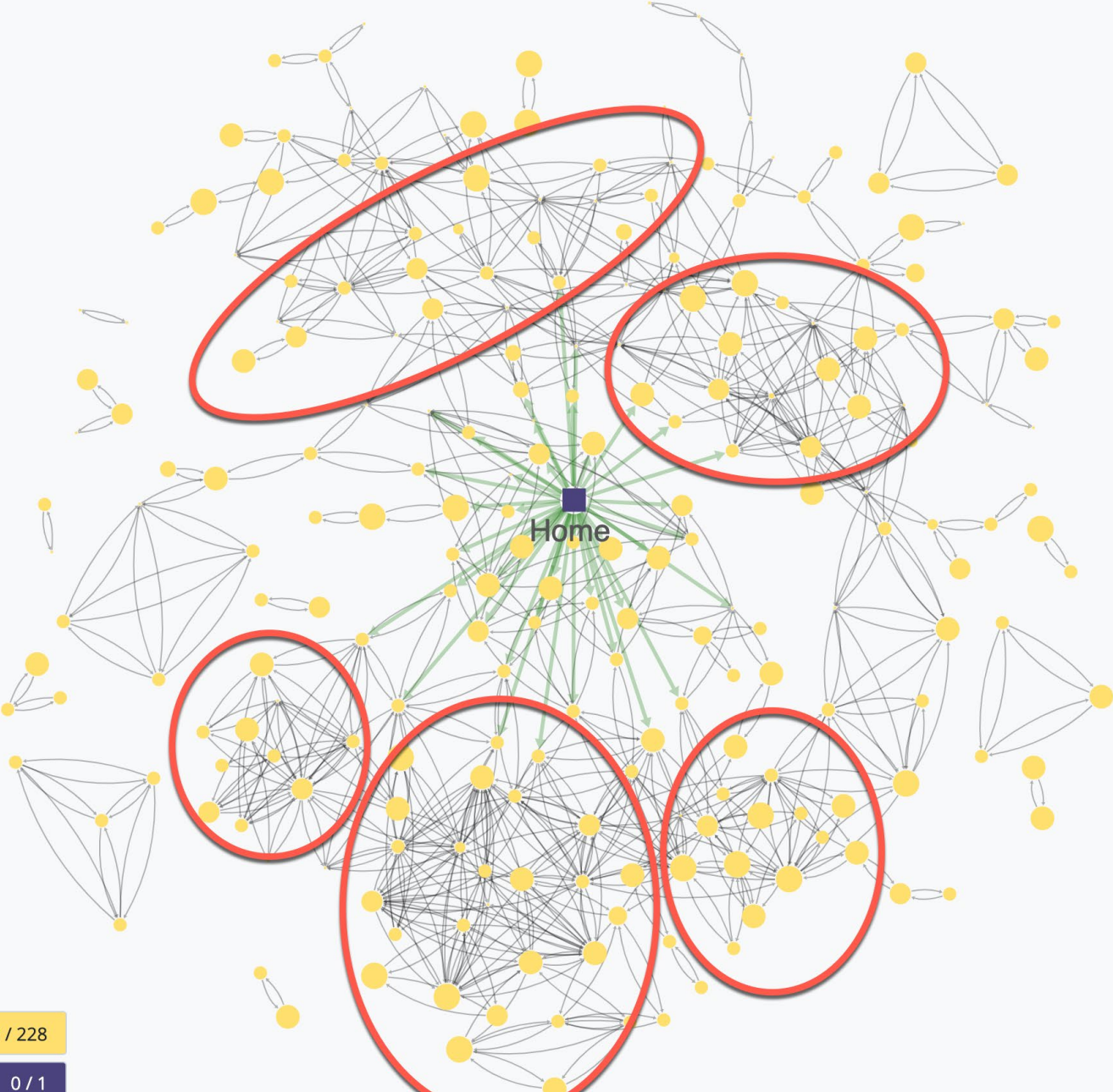
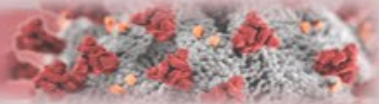
■ Cluster 3

analyzer digital protein sensor antigen

■ Cluster 5

antigen antibodies antibody aptamer lateral

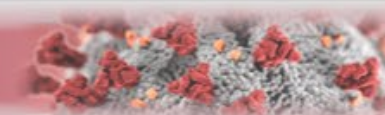
Project Clusters for Home Use



Elements

Project Submis... 0 / 228

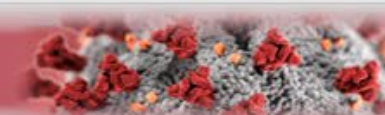
Search Term 0 / 1



Where are we now ?

The RADx Tech program created a tremendous body of knowledge that has only been partially tapped. With more than 700 completed applications, 139 Deep Dive assessments and over 500 independent faculty experts registered, some products are still in development. Others have already contributed to solving our present crisis.

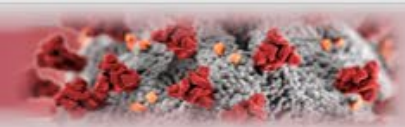
Emergency Use Authorized (EUA) Tests



TYPE OF TEST	TECHNOLOGY	SPECIMEN TYPE	REPORTED PPA & LIMIT OF DETECTION*	NUMBER OF TESTS w/FDA EUA	POINT OF CARE TESTS w/FDA EUA
Molecular tests	RNA Amplification, RT-PCR, Lamp, CRISPR, Next generation sequencing	Respiratory, Saliva	~85-100%, LoD: as low as 0.125 virus copies/ μ L	182	7
Antigen Detection tests	Lateral Flow, Chromatography, Fluorescence	Respiratory, Saliva	~85%-97% LoD: 10^2 TCID ₅₀ (100-10,000x less sensitive than molecular)	6	6
Other Serology tests (Antibody tests)	IgG & IgM detection (antibodies to the SARS-CoV-2 virus), detection of biomarkers	Blood	~90%-100%	56 serology tests authorized	1

*Estimates

Note: Only 2 tests are authorized for asymptomatic screening: Hologic Panther & LabCorp



- **Molecular tests:** 182 with EUA

- **7** are for Point of Care (POC)
(operating under a CLIA Certificate of Waiver)
 - BioFire Dx
 - Cepheid Xpert Xpress SARS CoV-2/Flu/RSV
 - Cepheid Xpert Xpress SARS CoV-2
 - Roche cobas SARS-CoV-2 & FluA/B cobas Liat
 - Abbott ID NOW COVID -19
 - Mesa Biotech Accula SARS-CoV-2
 - Cue Health Cue COVID-19 Test

- **Serology:** 56 with EUA

- **1** is for POC
 - Assure Tech LFA

- **Antigen:** 6 with EUA

- **All 6** are for POC
 - Access Bio LFA
 - Quidel Sofia 2 Flu+ SARS FIA
 - Abbott BinaxNOW COVID-19
 - LumiraDx LumiraDx SARS-CoV-2 Ag
 - Becton Dickinson BD Veritor System for Rapid Detection of SARS
 - Quidel Sofia SARS Antigen FIA

- **Note:** *some laboratories have EUA for laboratory developed tests (LDTs) for SARS-CoV-2. All of these labs are high complexity.*



Rapid Acceleration of Diagnostics (RADx)

QUESTIONS



OCTOBER 27

Closing the Testing Gap: A Panel Discussion on the Emerging Innovative Technologies and Their Impact on Current Testing Challenges

Moderated by Dr. Bruce Tromberg, Director of NIBIB

NOTE: New Start Time at 2:30 not 2P!!

Thanks to the Planning Committee:

Richard Creager, Albine Martin, Julie Wilkinson, Dan Marshak, Tania Fernandez, and Michael Masterman Smith



POCTRN

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