

How to Avoid Building an Airplane Mid Flight

Lab Medicine in the Face of Emerging Public Health Crises

SEPTEMBER 2023

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High Consequence Pathogen Response

Virology

Molecular Infectious Diseases



Objectives

Review the recent history of emerging/reemerging pathogens and challenges faced by laboratories

Describe the challenges of resolving differences in federal regulatory processes for test development compared to traditional clinical laboratory processes for assay development

Identify key stakeholders and important communication strategies for improved response and workflows for responding to emerging and/or reemerging pathogens



■ Concepts to Consider



Reactive vs Proactive



WHAT WE DO
NOW



WHAT WE WANT
TO DO



BARRIERS TO
SUCCESS



LONG TERM
SUSTAINABILITY



Emerging vs Re-emerging pathogens

New & unknown

- Scary/unknown
- Discovery before targeting
- Bad or mis-information complicates things

Old & known

- Neglected
- De-prioritized
- Shifting geographies
- Widely preventable

A blurred background image of a laboratory or hospital setting, showing various pieces of equipment and a window with a view of a building.

■ Emergency Use Authorization (EUA)

A historical perspective for future pandemics

Emergency Use Authorization



How does an EUA declaration impact assay development?



Lab challenges during EUA declarations

SARS-CoV-2
MPXV

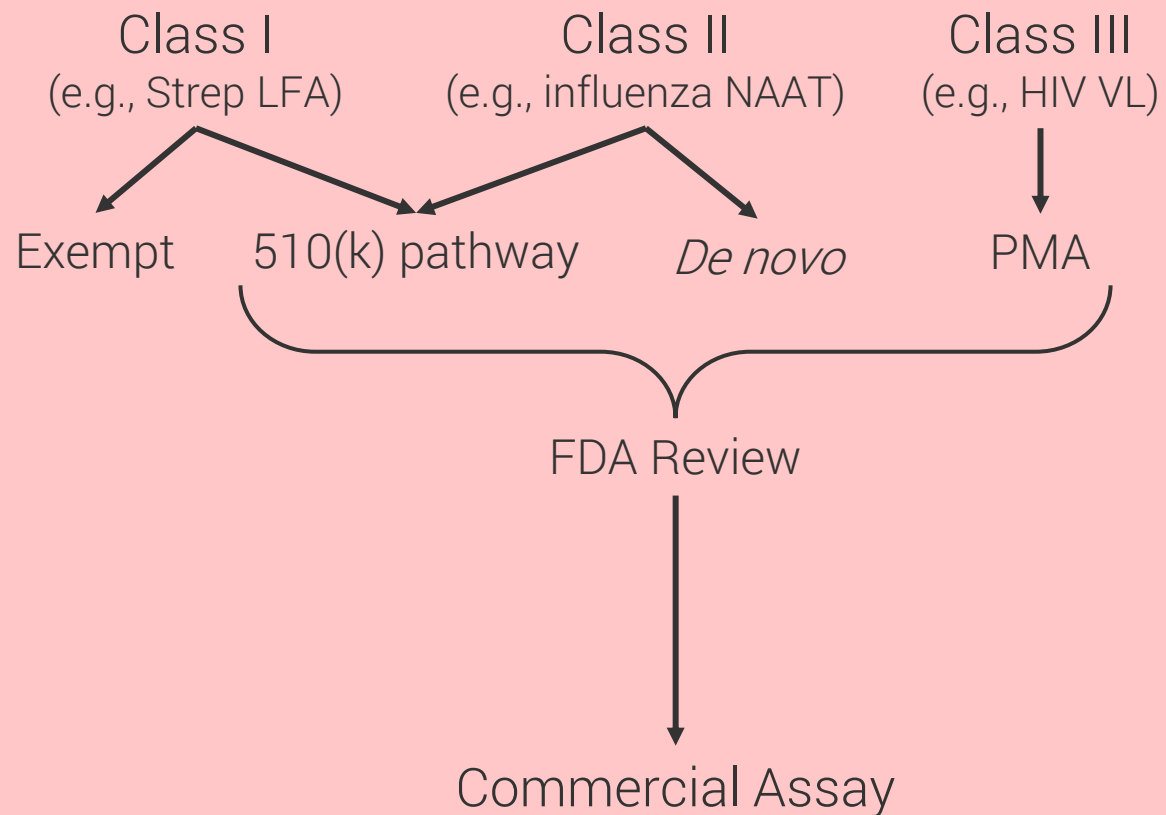


What happens when an EUA ends?

Traditional FDA Approval

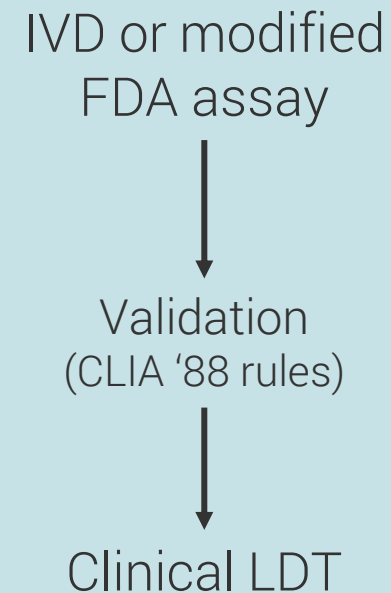
FDA Oversight

Manufacturer Assays



CMS Oversight

Lab Assays





The role of EUAs

Developed to address challenges faced during the 2001 US anthrax attacks



Congress drafted legislation allowing FDA to review and *provisionally* approve medical countermeasures



A national emergency must exist and be declared

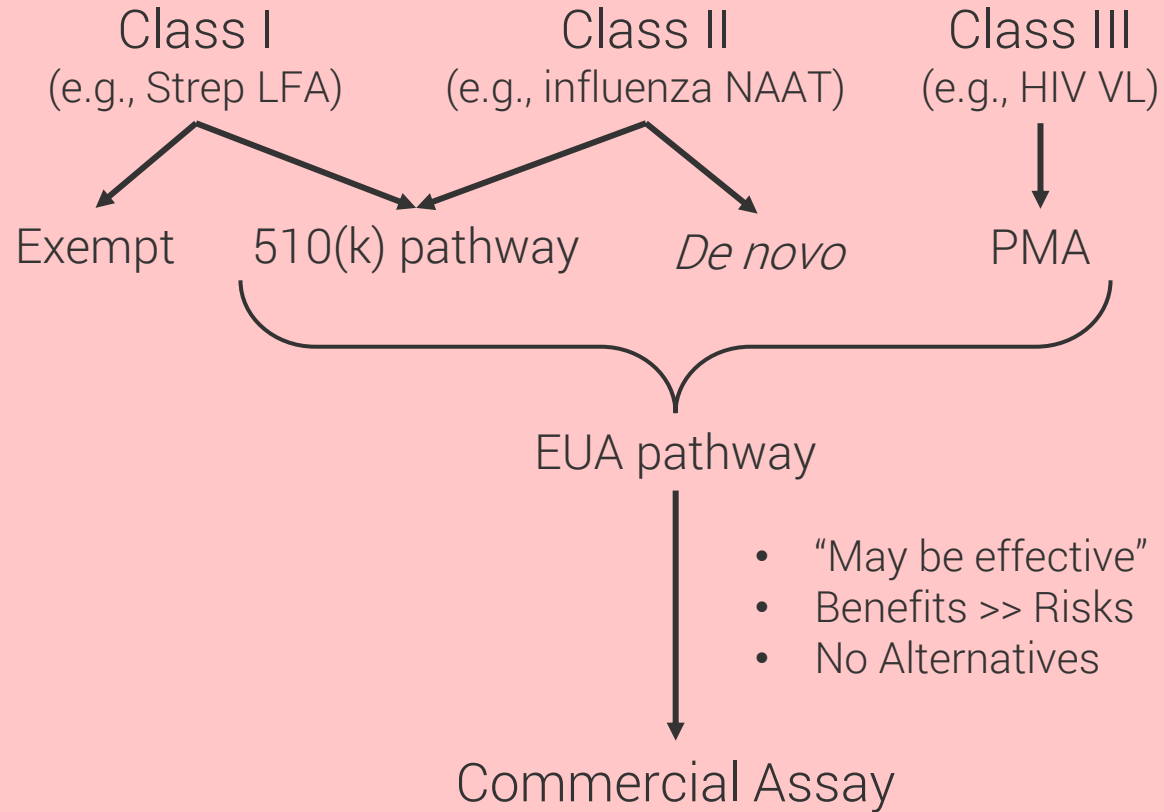


EUA declaration signed by the DHHS secretary

EUA Approval Pathway

FDA Oversight

Manufacturer Assays



CMS Oversight

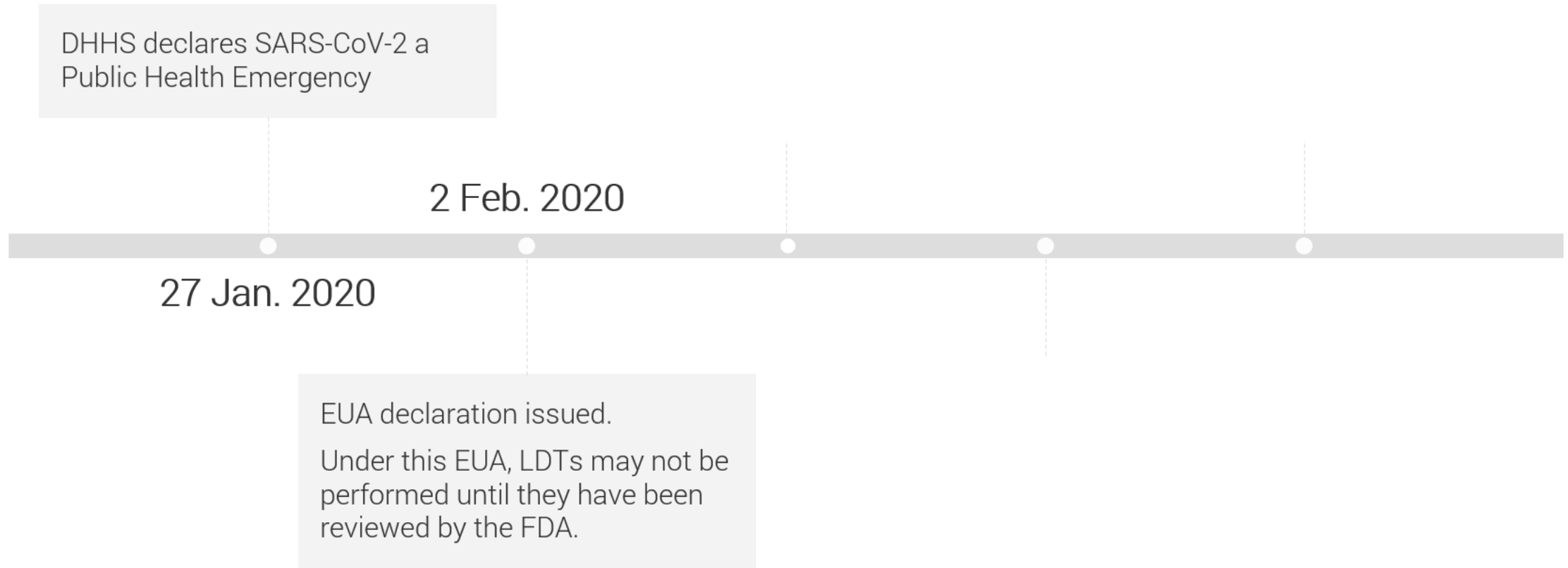
Lab Assays

IVD or modified
FDA assay

Validation
(CLIA '88 rules)

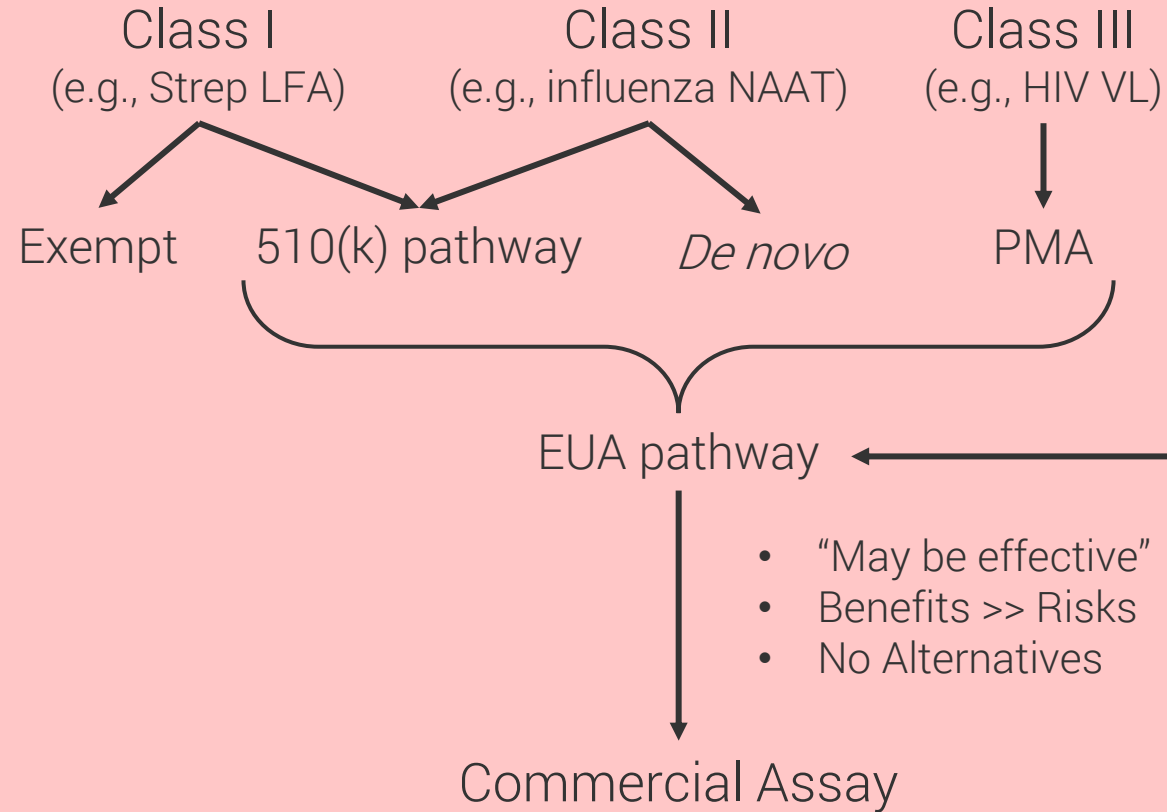
Clinical LDT

EUA and SARS-CoV-2



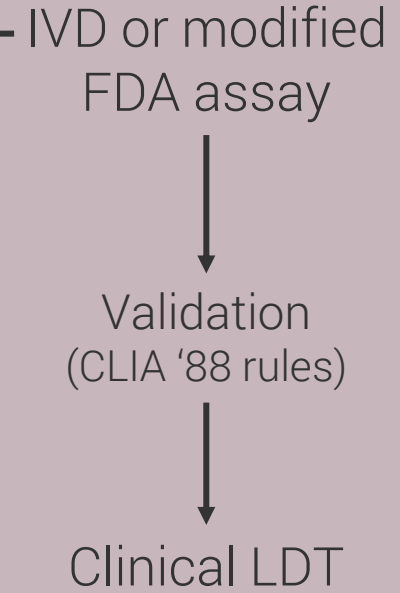
FDA Oversight

Manufacturer Assays

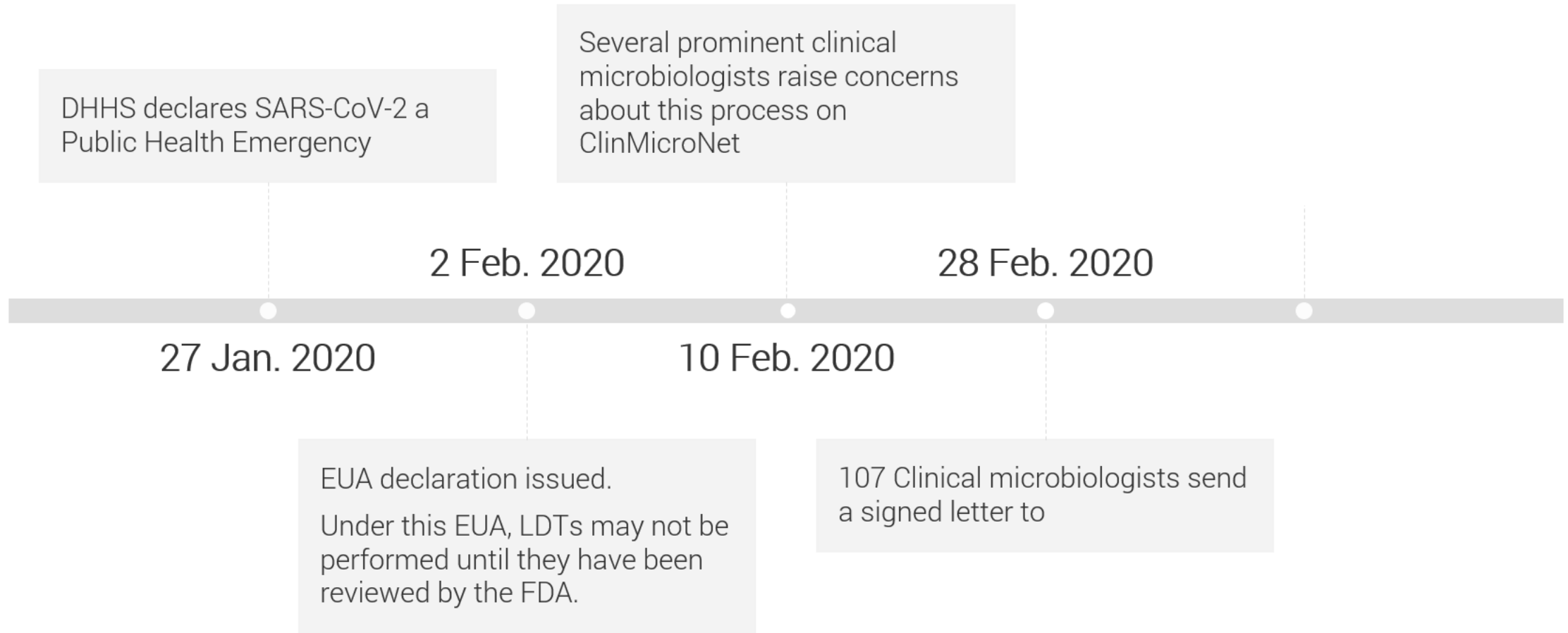


CMS Oversight

Lab Assays



EUA and SARS-CoV-2



The Honorable Frank Pallone
Chairman
House Committee on Energy & Commerce
U.S. House of Representatives
Washington, DC 20515

The Honorable Greg Walden
Ranking Member
House Committee on Energy and Commerce
U.S House of Representatives
Washington, DC 20510

The Honorable Lamar Alexander
Chairman
Senate Health, Education, Labor and Pensions
Committee
U.S. Senate
Washington, DC 20510

The Honorable Patty Murray
Ranking Member
Senate Health, Education, Labor and Pensions
Committee
U.S. Senate
Washington, DC 20510

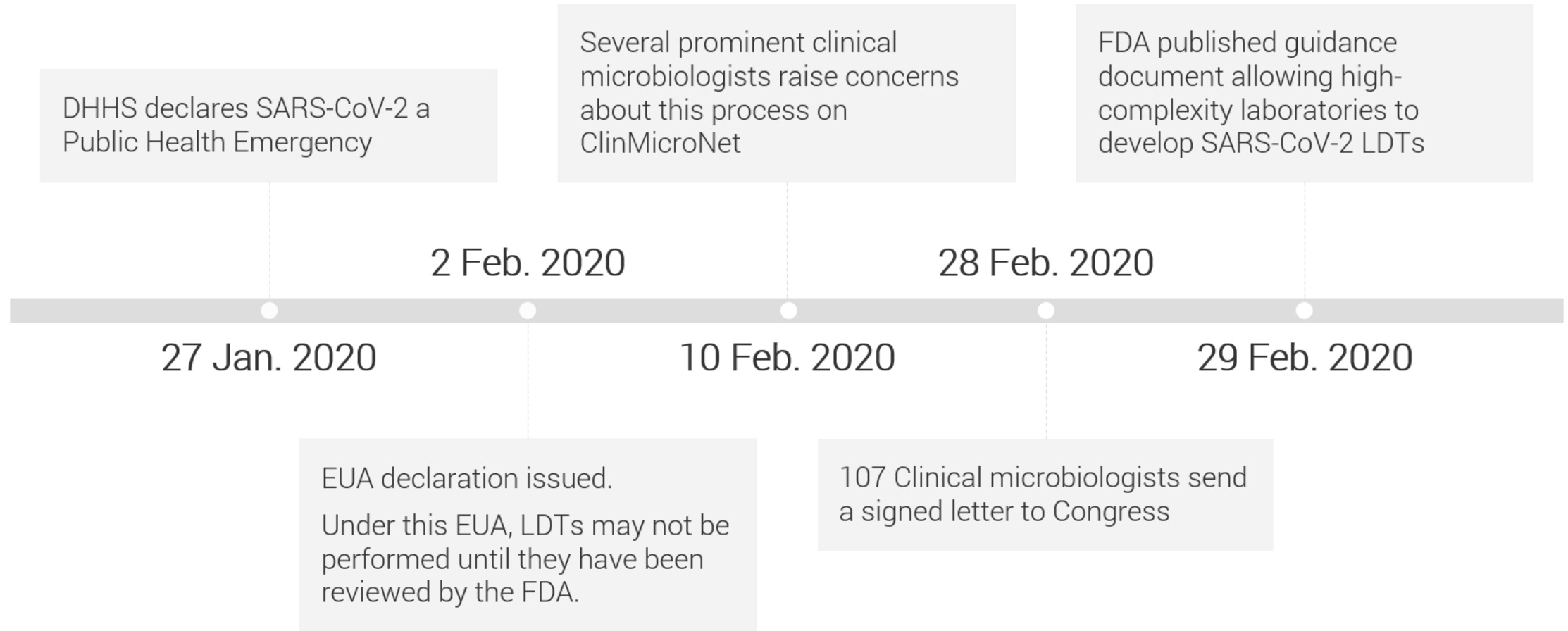
February 28, 2020

Dear Chairman Pallone, Ranking Member Walden, Chairman Alexander and Ranking Member Murray:

On behalf of CLIA-certified U.S. clinical diagnostic laboratories, we write to request the ability to perform high-complexity laboratory developed tests (LDTs) for SARS-CoV-2 in our clinical laboratories under CMS/CLIA rules as opposed to being restricted to the current FDA Emergency Use Authorization (EUA) pathway.

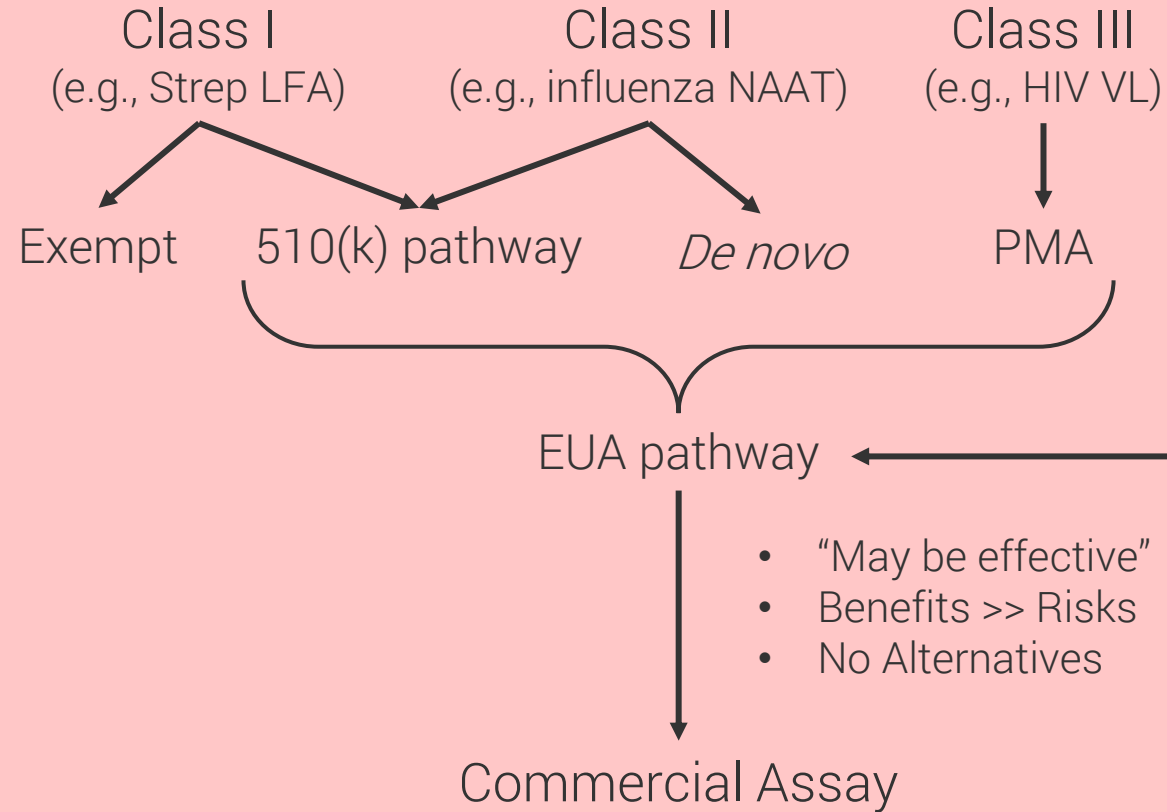
As you are aware, COVID-19 presents a major threat to the public health of the United States. Diagnostic testing for the virus causing COVID-19 (SARS-CoV-2) is a critical component of our nation's response to the current pandemic. The widespread availability of diagnostic testing enables rapid identification of infected individuals so they can be quickly isolated to prevent onward transmission of the virus in the general population and healthcare settings.

EUA and SARS-CoV-2



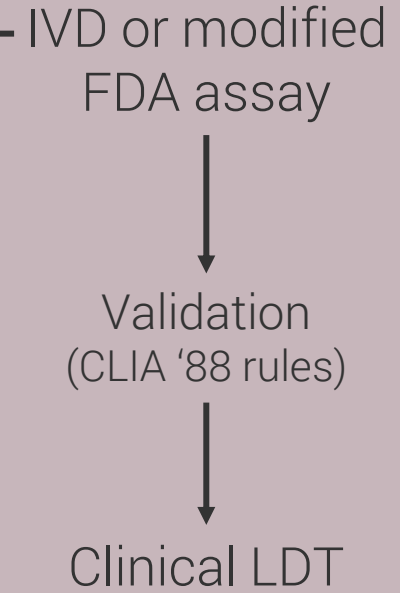
FDA Oversight

Manufacturer Assays

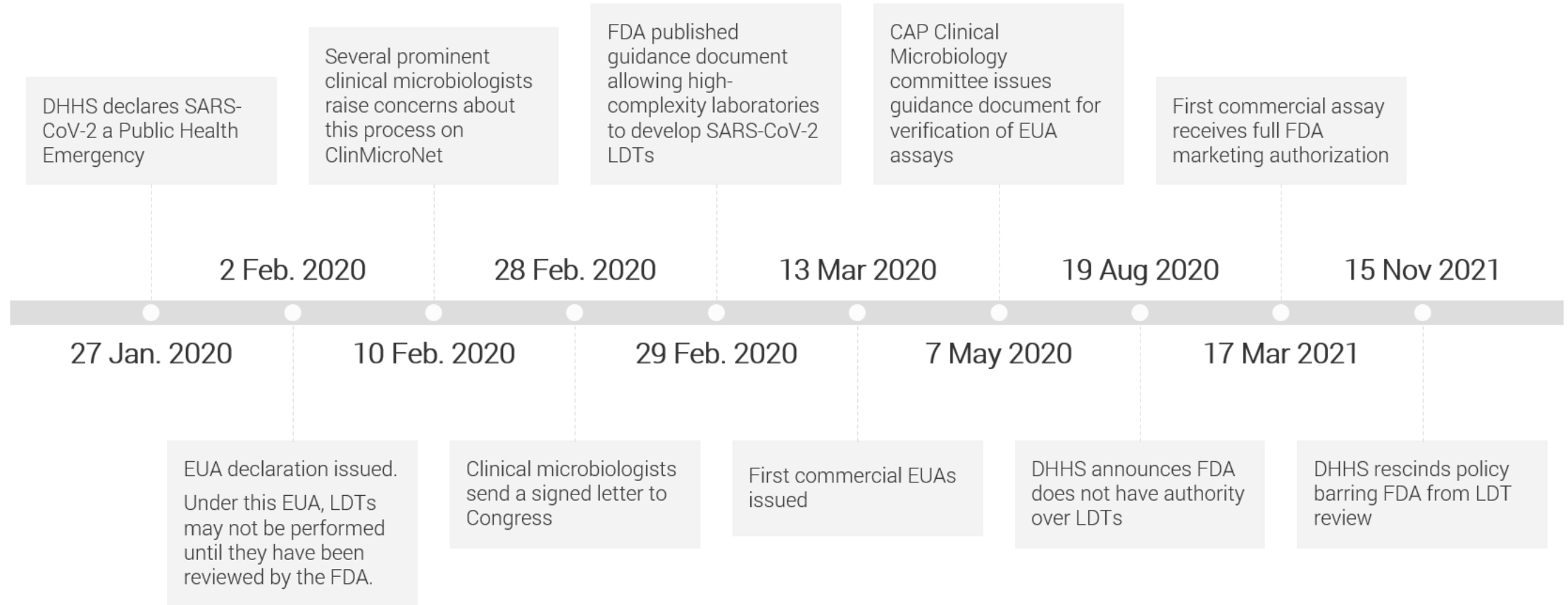


CMS Oversight

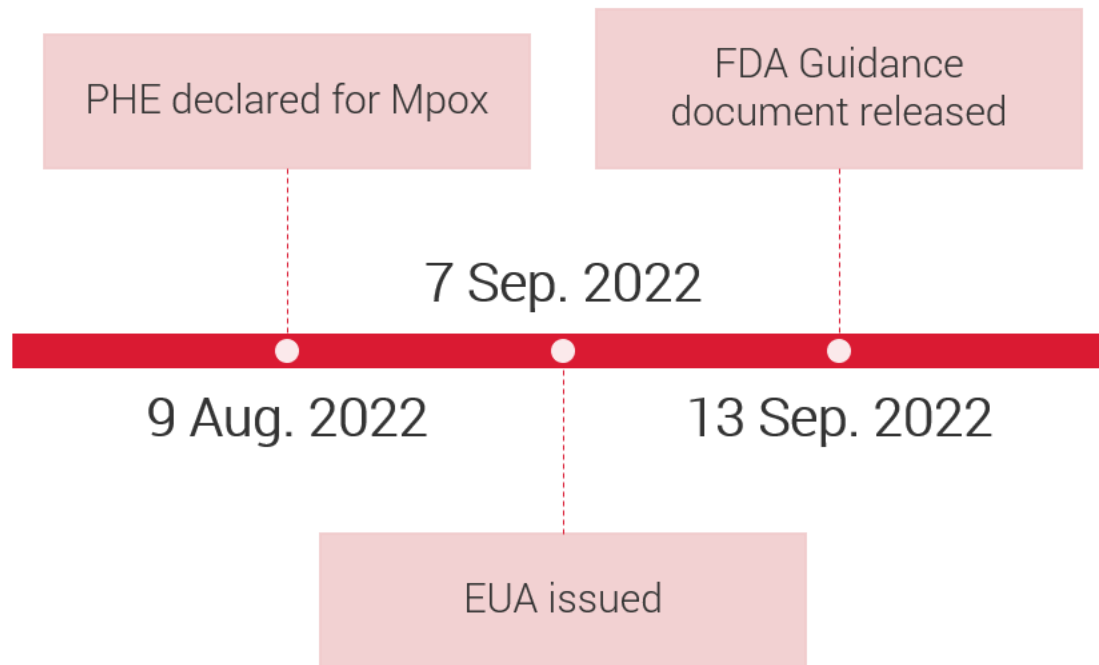
Lab Assays



EUA and SARS-CoV-2



EUA and MPXV



- FDA does not intend to object to mpox LDTs when:
 - » The test is PCR based
 - » The test uses lesion swabs
 - » The test is appropriately validated
 - » The lab notifies the FDA within five days of validation

Should high-complexity clinical laboratories be allowed to expand testing?

Expanding capacity for diagnosis and surveillance of mpox

Laboratory testing for the monkeypox virus

Interim guidance

23 May 2022

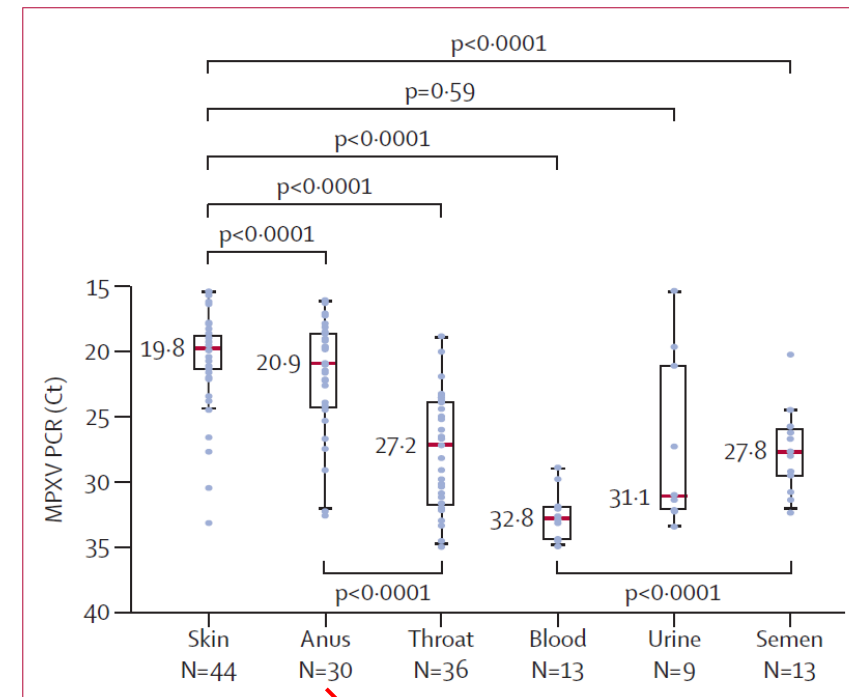


Annex. Specimen collection and storage

Specimen type	Collection materials	Storage temperature	Collection purpose
Skin lesion material, including: – swabs of lesion exudate – lesion roofs – lesion crusts	Dacron or polyester flocked swabs with VTM or dry swab	Refrigerate (2–8 °C) or freeze (-20 °C or lower) within 1 hour of collection; -20°C or lower after 7 days	Recommended for diagnosis
Oropharyngeal swab	Dacron or polyester flocked swabs with VTM or dry swab	See above	Recommended for diagnosis if feasible, in addition to skin lesion material
Rectal and/or genital swabs	Dacron or polyester flocked swabs with VTM or dry swab	See above	To be considered for research (following ethics guidelines)
Urine	Sterile collection tube	See above	To be considered for research (following ethics guidelines)
Semen	Sterile collection tube	Room temperature for <1h (then -20 °C or lower)	To be considered for research (following ethics guidelines)
Whole blood	Sterile collection tube with EDTA	See above	To be considered for research (following ethics guidelines)
Serum	Serum-separating tubes	Refrigerate (2–8 °C) or freeze (-20 °C or lower) within 1 hour of collection; -20°C or lower after 7 days	To be considered for serology to aid diagnosis or research (following ethics guidelines)
Plasma	collection tube with EDTA	See above	To be considered for serology to aid diagnosis or research (following ethics guidelines)

Viral loads in clinical samples of men with monkeypox virus infection: a French case series

Romain Palich, Sonia Burrel, Gentiane Monsel, Agathe Nouchi, Alexandre Bleibtreu, Sophie Seang, Vincent Bérot, Cécile Brin, Ariane Gavaud, Yara Wakim, Nagisa Godefroy, Antoine Fayçal, Yanis Tamzali, Thomas Grunemwald, Michel Ohayon, Eve Todesco, Valentin Leducq, Stéphane Marot, Vincent Calvez, Anne-Geneviève Marcelin, Valérie Pourcher




Avg Ct w/ ulcer: 19.6
Avg Ct w/o ulcer: 25.3

Expanding capacity for diagnosis and surveillance of mpox

Letters | October 2022

Detection of Monkeypox Virus in Anorectal Swabs From Asymptomatic Men Who Have Sex With Men in a Sexually Transmitted Infection Screening Program in Paris, France FREE

Valentine Marie Ferré, PharmD , Antoine Bachelard, MD, Meryem Zaidi, BSc, ... [View all authors +](#)

[Author, Article, and Disclosure Information](#)





Journal of Clinical Virology

Volume 164, July 2023, 105493



Prevalence of Mpox (Monkeypox) in patients undergoing STI screening in northern California, April-September 2022

Caitlin A. Contag^a  , Zachary T. Renfro^b, Jacky Lu^c, Sa Shen^d, Abraar Karan^a, Daniel Solis^c, ChunHong Huang^c, Malaya K. Sahoo^c, Fumiko Yamamoto^c, Morris S. Jones^e, Jennifer Lin^f, Vivian Levy^{a, f}, Benjamin A. Pinsky^{a, c}

Variable	MSM With No Symptoms of MPXV Infection
Total number of MSM visiting between 5 June and 11 July 2022	323
<i>C trachomatis</i> infections detected on anal swab, n/N (%)	32/323 (9.9)
<i>N gonorrhoeae</i> infections detected on anal swab, n/N (%)	24/323 (7.4)
<i>C trachomatis</i> and <i>N gonorrhoeae</i> co-infection detected on anal swab, n/N (%)	8/323 (2.5)
<i>C trachomatis</i> infections detected on first-void urine sample or urethral swab, n/N (%)	6/323 (1.9)
<i>N gonorrhoeae</i> infections detected on first-void urine sample or urethral swab, n/N (%)	3/323 (0.9)
<i>C trachomatis</i> and <i>N gonorrhoeae</i> co-infection detected on first-void urine sample or urethral swab, n/N (%)	1/323 (0.3)
MPXV-positive test result, n/N (%)	13/200* (6.5)

Results

- 7 MPXV+ patients w/o history of mpox
- 4/7 were cisgender women who reported only heterosexual activity

6.5% of MSM undergoing STI screening had MPXV detected from rectal swabs

What happens when an EUA expires?

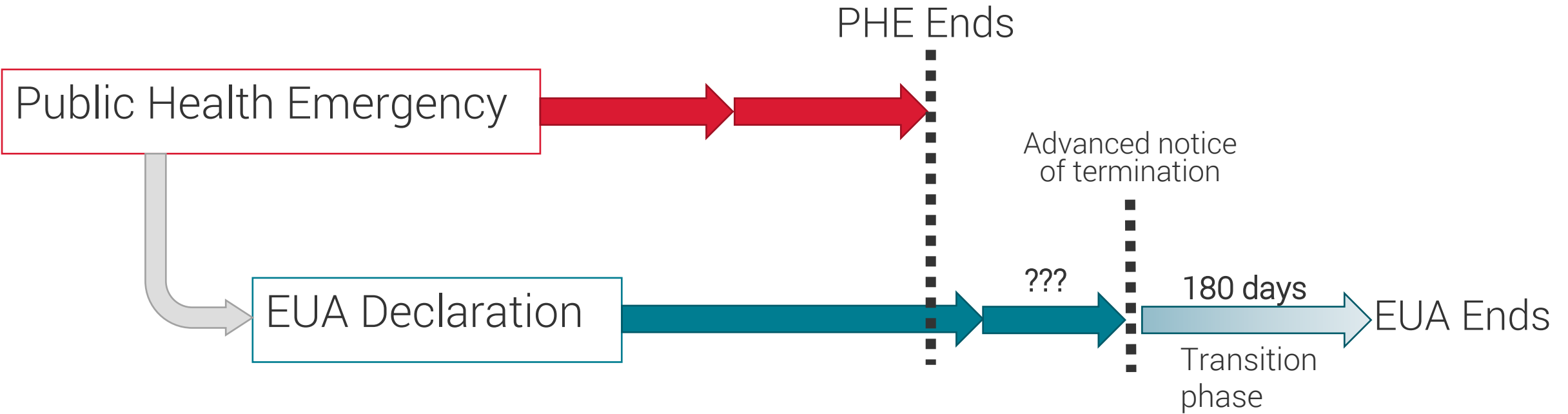
TABLE 1
Timeline of emergency use authorization declarations

Emergency	EUA Effective	EUA Terminated	Diagnostic EUAs	Total EUAs ^a
<i>Bacillus anthracis</i>	27/01/2005	ongoing	0	3
2009 H1N1 Influenza virus	26/04/2009	23/06/2010	18	21
Highly Pathogenic Avian Influenza (H7N9)	19/04/2013	ongoing	3	3
MERS Coronavirus	05/06/2013	ongoing	2	2
Ebola virus	04/08/2014	ongoing	13	13
Enterovirus D68	06/02/2015	20/02/2023	1	1
Zika virus	28/09/2016	ongoing	20	20
SARS-CoV-2	04/02/2020	ongoing	443	664
Mpox virus	07/09/2022	ongoing	8	9

^a Includes IVDs, devices, therapeutics, and other medical countermeasures.
Data current as of 4/27/2023.

EUA Timeline

Transition Plan for Medical Devices Issued Emergency Use Authorizations (EUAs) Related to Coronavirus Disease 2019 (COVID-19)



<https://www.fda.gov/media/155039/download>

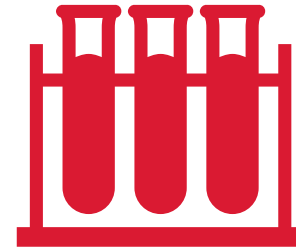
What happens when an EUA expires?



For Manufacturers

Assays must be submitted for review by traditional FDA pathways

If the assay is not submitted for review, it is no longer approved for clinical use



For Laboratories

Any COVID LDTs will be treated as other LDTs

For EUA assays, some verification studies may be repeated

Any modification to EUA assays following termination will require validation studies



■ Partnering with Public Health

Get to know thy neighbor...sooner than later



Do's and Don'ts of Interacting with Public health

Don't	Be strangers
Don't	Assume you understand each other
Do	Offer to collaborate
Do	Share resources when possible
Do	Communicate early and often



Don't Be Strangers



Pick up the phone



Set up a meeting



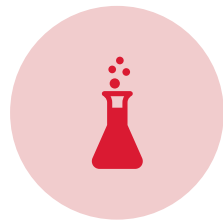
Form a taskforce/team



Stay in constant communication



Don't Assume You Understand Each Other



Tour each other's lab



Learn each other's basic processes



Learn each other's limitations



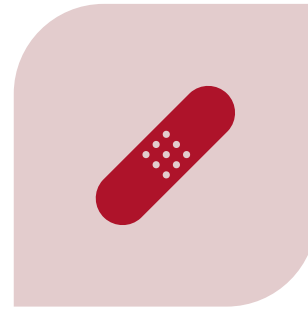
Meet each other's technical staff



Do Offer to Collaborate



FIND MUTUAL INTERESTS



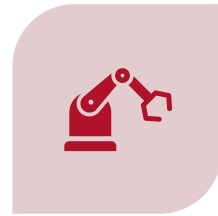
FIND MUTUAL PAIN
POINTS



EXPLORE
COMPLEMENTARY ROLES



Do Share Resources When Possible



INSTRUMENTATION



PROCEDURES



TRICKS/EXPERIENCE



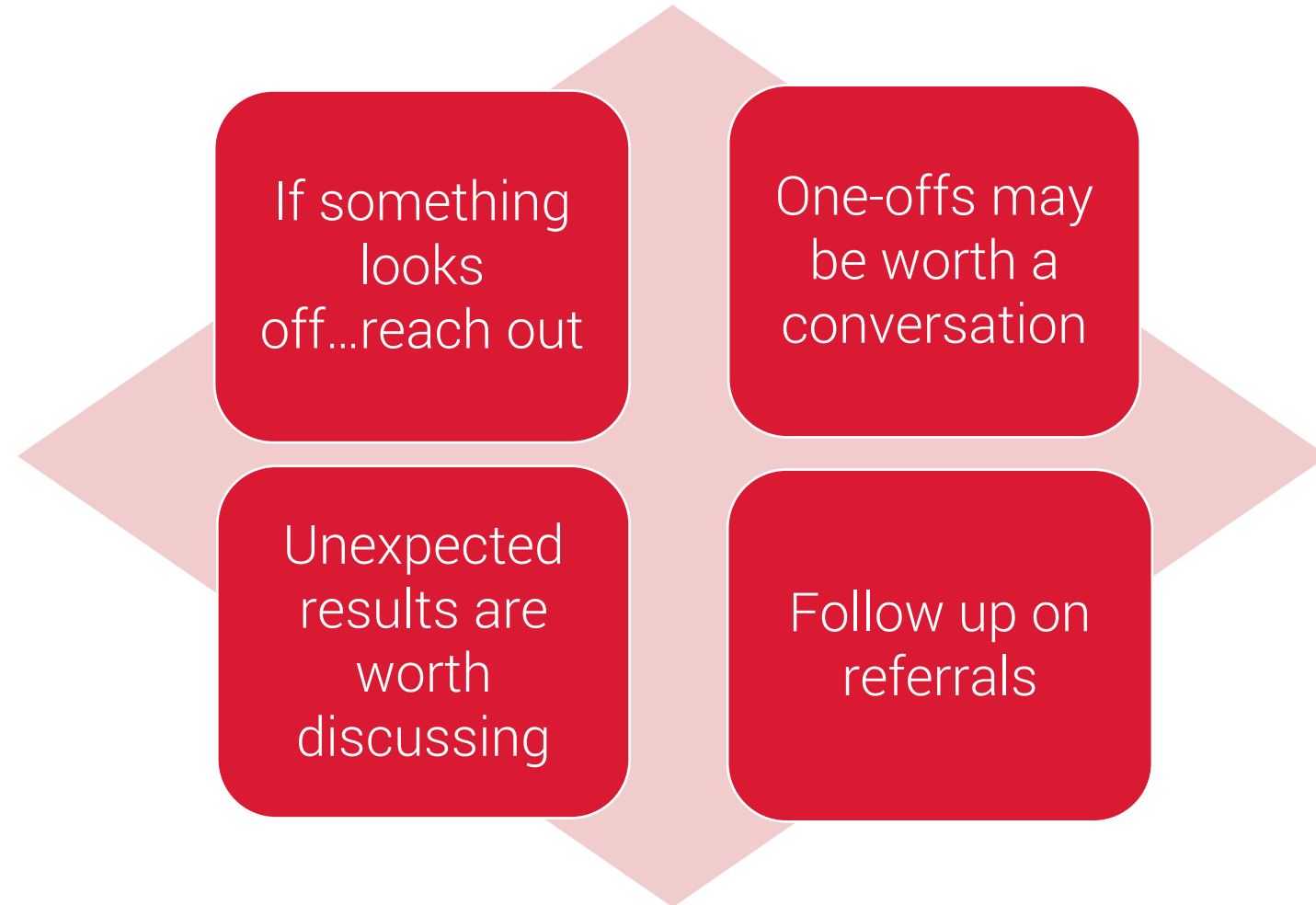
SPECIMENS



CONTACTS/CONNECTIONS



Do Communicate Often and Early





Partnering With & Beyond Public Health

Other Labs and Federal Agencies



Who Else Can You Partner With?



LOCAL HOSPITALS



OTHER MEDICAL
SYSTEMS IN YOUR
REGION



REGIONAL
REFERENCE LABS



NATIONAL
REFERENCE LABS

Example of Success

Lessons learned from Zika virus

- CDC's DLS (Division of Laboratory Systems) spearheads private-public partnership thru an MOU
 - » National Reference Labs (*via* ACLA)
 - » Federal Agencies (CSTE, APHL, CDC, FDA)
 - » Other associations (AdvaMed, AMP, NILA)

Salerno RM, Chaitram J, Andreadis JD. Building a Public-Private Partnership to Enhance Laboratory Preparedness and Response in the United States. *Disaster Med Public Health Prep.* 2021 Oct;15(5):657-660



DLS Improves Communications

Optimizes LOCS – Laboratory Outreach Communication System

More frequent & timely communications in “real-time”

Ability to engage surge capacity response with partners

Regularly schedule informative webinars

Quarterly call with partners

ARUP Creates Defined Roles

- Partners now have defined contacts
- New director roles interface with outside agencies

Director of Emerging Public Health Crises



Marc Couturier

Benjamin Bradley



Director of High Consequence Pathogen Response





■ Organic Communications from
Within the Lab Community

Multipronged approach



ClinMicroNet



International group of clinical microbiology laboratory directors



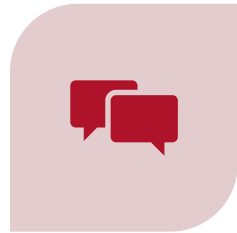
Semi-private listserv hosted by ASM

Criteria for membership:

- Doctoral-level clinical microbiology laboratory director
- or Laboratory manager/expert with national standing and peer recognition



ClinMicroNet



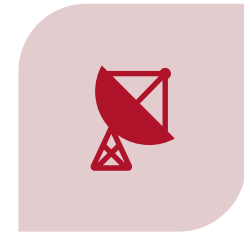
DISCUSS TRENDS



SHARE CONCERNS



REPORT UNUSUAL
FINDINGS



CAN SERVE AS
"OUTBREAK RADAR"

All email-based...real-time communication



Rapid Publication of Information

Fast-track
publications

Crowd-sourcing
data

Professional
committees
drafting guidance,
near real-time

The Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Antigen Testing

Mary K. Hayden,^{1,2} Kimberly E. Hanson,³ Janet A. Englund,⁴ Francesca Lee,⁵ Mark J. Lee,⁶ Mark Loeb,⁷ Daniel J. Morgan,⁸ Robin Patel,⁹ Abdallah El Alayli,¹⁰ Ibrahim K. El Mikati,¹¹ Shahnaz Sultan,¹² Yngve Falck-Ytter,^{13,14} Razan Mansour,¹⁵ Justin Z. Amarin,¹⁶ Rebecca L. Morgan,^{13,17} M. Hassan Murad,¹⁸ Payal Patel,¹⁹ Adarsh Bhimraj,²⁰ and Reem A. Mustafa²¹

College of American Pathologists (CAP) Microbiology Committee Perspective: the Need for Verification Studies

This letter has a response. [VIEW RESPONSE](#)

Authors: [Christina M. Wojewoda](#), [Neil W. Anderson](#), [Romney M. Humphries](#), [Isabella W. Martin](#), [Blaine A. Mathison](#), [Allison R. McMullen](#), [Frederick S. Nolte](#), [SHOW ALL \(19 AUTHORS\)](#), [Bobbi S. Pritt](#) | [AUTHORS INFO & AFFILIATIONS](#)

The Role of Antibody Testing for SARS-CoV-2: Is There One?

[Elitza S. Theel](#)^a, [Patricia Slev](#)^{b,c}, [Sarah Wheeler](#)^d, [Marc Roger Couturier](#)^{b,c}, [Susan J. Wong](#)^e, [Kamran Kadkhoda](#)^f

JOURNAL ARTICLE

College of American Pathologists (CAP) Microbiology Committee Perspective: Caution Must Be Used in Interpreting the Cycle Threshold (Ct) Value FREE

[Daniel Rhoads](#), [David R Peaper](#), [Rosemary C She](#), [Frederick S Nolte](#), [Christina M Wojewoda](#), [Neil W Anderson](#), [Bobbi S Pritt](#) ✉

Considerations from the College of American Pathologists for Implementation of an Assay for SARS-CoV-2 Testing after a Change in Regulatory Status

Authors: [David R. Peaper](#), [Daniel D. Rhoads](#), [Kaede V. Sullivan](#), [Marc R. Couturier](#), [Romney M. Humphries](#), [Isabella W. Martin](#), [Frederick S. Nolte](#), [Marie-Claire Rowlinson](#), [Rosemary C. She](#), [Patricia J. Simner](#), [Elitza S. Theel](#), [Christina M. Wojewoda](#) ✉ | [AUTHORS INFO &](#)

Understanding, Verifying, and Implementing Emergency Use Authorization Molecular Diagnostics for the Detection of SARS-CoV-2 RNA

[Stephanie L. Mitchell](#)^a, [Kirsten St. George](#)^b, [Daniel D. Rhoads](#)^c, [Susan M. Butler-Wu](#)^d, [Vaishali Dharmarha](#)^e, [Peggy McNult](#)^e, [Melissa B. Miller](#)^f, on behalf of the American Society for Microbiology Clinical and Public Health Microbiology Committee



Rapid Publication Requires Contacts

See previous strategies w/Public Health



KNOW YOUR PEERS
AND HOW TO
CONTACT THEM



MAKE PHONE
CALLS TO
COLLEAGUES



LEARN WHO YOU
CAN WORK WITH
EFFECTIVELY



BUILD TRUST

A blurred background image of a laboratory or hospital setting, showing various pieces of equipment and a window with a view of a building.

■ What can('t) you do?

Establishing and understanding the limits of your lab

Questions to ask about your lab

Facilities

Is there space?
What are your certifications?

Personnel

Are there protocols?
Are personnel trained?

Available assays

Establishing the minimum
Travelers with fever?
Post-outbreak maintenance

Questions to ask others



- » What testing do you have available?
- » Are there plans to build capacity?
- » Can I send you this isolate for rule out?



Lab Response Network

- » Who is your LRN reference lab
- » Sentinel vs. Reference lab

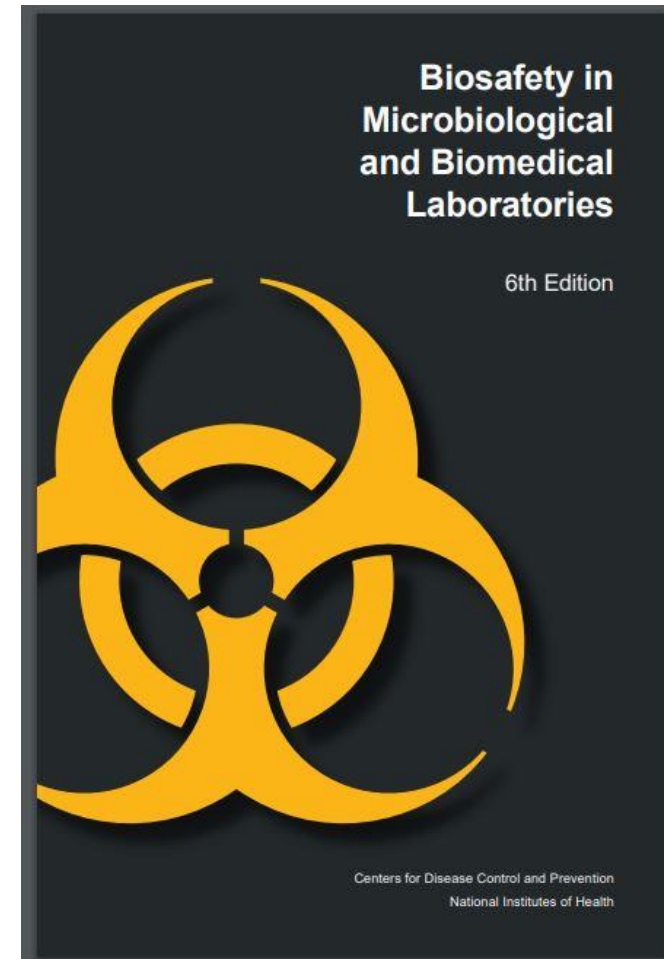


Division of Laboratory Systems

- » Available validation materials
- » Protocols
- » Communication

Questions to ask about the pathogen

- BMBL is useful resource
- For each pathogen ask:
 - » Specimen handling
 - » What tests can be performed
 - » Risk mitigation strategies
- Know your assay!

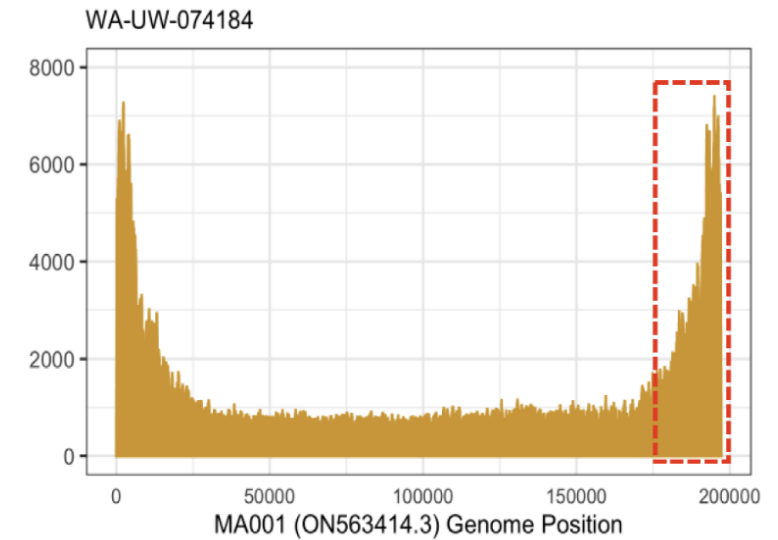
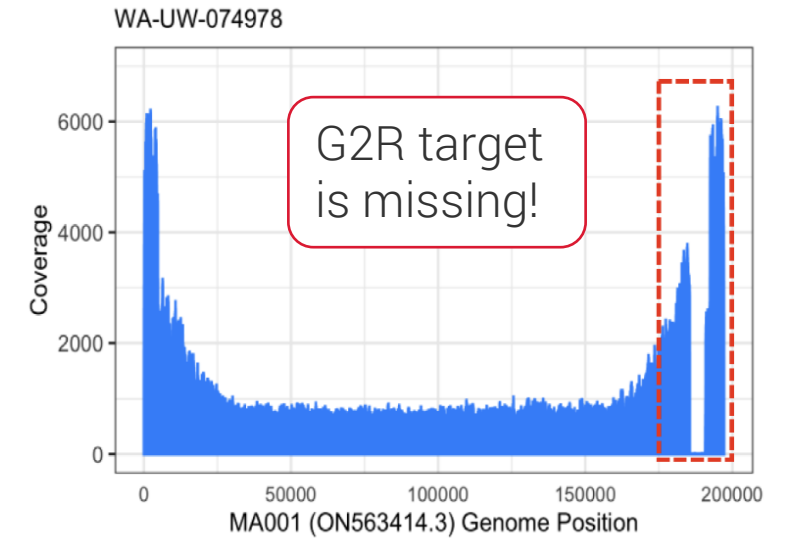


Know your assay!

Viruses	Assay Target			
	E9L	E9L-NVO	F3L	G2R
Molluscum				
Variola*				
Vaccinia				
MPXV clade I*				
MPXV clade II				

Virus

Not Detected
Detected



<https://doi.org/10.3390/v14112393>



What will you do?

- There is no one-size-fits-all answer
- Define the boundaries of your gray zone
- Expand the lines of thinking
 - » “Yes, and...”
 - » “No, and...”

A blurred background image of a laboratory or hospital setting, showing various pieces of equipment and a window with a view of a building.

■ Ok, so you think you have a plan...

Now...go.



Re-emerging Examples

EV D68

Polio

Measles

Mumps

TB

Malaria



Malaria in the US



Failing competency for microscopy

Are results accurate?
Who are your resources?



1 FDA cleared rapid antigen

Source specimens to verify?



1 FDA cleared NAAT
(as syndromic panel)

Source specimens to verify
Viable for just malaria?



Reference lab NAATs as
LDTs

Limited availability
Not intended for diagnosis
Pathway for testing/submission?



ARUP is a nonprofit enterprise of the University of Utah and its Department of Pathology.