

Clinical Laboratory COVID-19 Response Call

Monday, July 18, 2022, at 3:00PM ET

- **Welcome**
 - Sean Courtney, Division of Laboratory Systems, CDC
- **SARS-CoV-2 Variants Update**
 - Clint Paden, Division of Viral Diseases, CDC
- **A System for Early Detection and Monitoring of COVID Variants**
 - Eric Lai, Rapid Acceleration of Diagnostics (RADx) Variant Task Force, National Institutes of Health (NIH)
- **FDA Update**
 - Tim Stenzel, US Food and Drug Administration (FDA)
- **Monkeypox Update**
 - Christina Hutson, Monkeypox Response, CDC

About DLS

Vision

Exemplary laboratory science and practice drive clinical care and public health.

Mission

Improve public health surveillance and practice as well as patient outcomes by advancing clinical laboratory quality and safety, data and biorepository science, and workforce competency.

Four Goal Areas



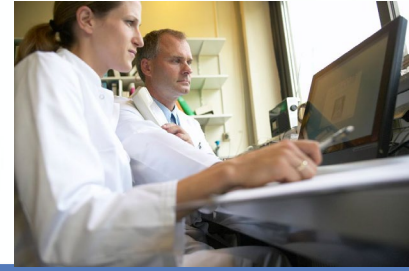
Quality Laboratory Science

- Improve the quality and value of laboratory medicine and biorepository science for better health outcomes and public health surveillance



Highly Competent Laboratory Workforce

- Strengthen the laboratory workforce to support clinical and public health laboratory practice



Safe and Prepared Laboratories

- Enhance the safety and response capabilities of clinical and public health laboratories



Accessible and Usable Laboratory Data

- Increase access and use of laboratory data to support response, surveillance, and patient care

Monkeypox Guidance

Laboratory Procedures & Biosafety Guidelines

How to Report Test Results

The screenshot shows the CDC website page for Monkeypox Laboratory Procedures and Biosafety Guidelines. The breadcrumb trail is CDC > Poxvirus > Monkeypox > Laboratories. The main heading is "Laboratory Procedures and Biosafety Guidelines". The left sidebar includes links for "About Monkeypox", "U.S. Outbreak 2022: Situation Summary", "Signs & Symptoms", "How it Spreads", "Prevention", "Vaccines", "Treatment", "Sexual Health", "Healthcare Professionals", "Laboratories", "Lab Procedures & Biosafety", and "How to Report Test Results". The main content area is titled "Routine Chemistry, Hematology, and Urinalysis in Hospitals or Clinical Laboratories". It includes a paragraph about testing for monkeypox virus infection and a list of non-lesion specimens. The right sidebar lists "On This Page" topics: "Routine Chemistry, Hematology, and Urinalysis in Hospitals or Clinical Laboratories", "Clinical Pathology, Molecular Testing, and Analysis of Bacterial or Mycotic Cultures", "Manipulating Diagnostic Specimens Suspected to Contain Monkeypox Virus", "Culturing Specimens for Monkeypox Virus", "Disposal of Waste", "Select Agent Regulations", and "Monitoring Healthcare Workers Exposed".

The screenshot shows the CDC website page for Monkeypox How to Report Test Results. The breadcrumb trail is CDC > Poxvirus > Monkeypox > Laboratories. The main heading is "How to Report Results from Orthopoxvirus, Non-Variola Orthopoxvirus, and Monkeypox Virus Laboratory Diagnostic Testing". The left sidebar includes links for "About Monkeypox", "U.S. Outbreak 2022: Situation Summary", "Signs & Symptoms", "How it Spreads", "Prevention", "Vaccines", "Treatment", "Sexual Health", "Healthcare Professionals", "Laboratories", "Lab Procedures & Biosafety", and "How to Report Test Results". The main content area is titled "Introduction" and "Who should report". The "Introduction" section states that the public health response depends on comprehensive laboratory testing and result reporting. The "Who should report" section includes a list of reporting requirements. The right sidebar lists "On This Page" topics: "Who should report", "What to report", "How to report", "Using standard terminology", and "Assistance with electronic reporting".

<https://www.cdc.gov/poxvirus/monkeypox/lab-personnel/report-results.html>

<https://www.cdc.gov/poxvirus/monkeypox/lab-personnel/lab-procedures.html>

Clinical Laboratory Biosafety Gaps: Lessons Learned



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REVIEW



Clinical Laboratory Biosafety Gaps: Lessons Learned from Past Outbreaks Reveal a Path to a Safer Future

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<https://stacks.cdc.gov/view/cdc/118337>

Laboratory Communications Toolkit

Communication strategies help simplify the process of translating complex information into meaningful messages for your audience.

OneLab's Laboratory Communications toolkit helps laboratories develop plain language communication strategies.

This job aid is available at www.cdc.gov/labtraining/onelab/network.html.

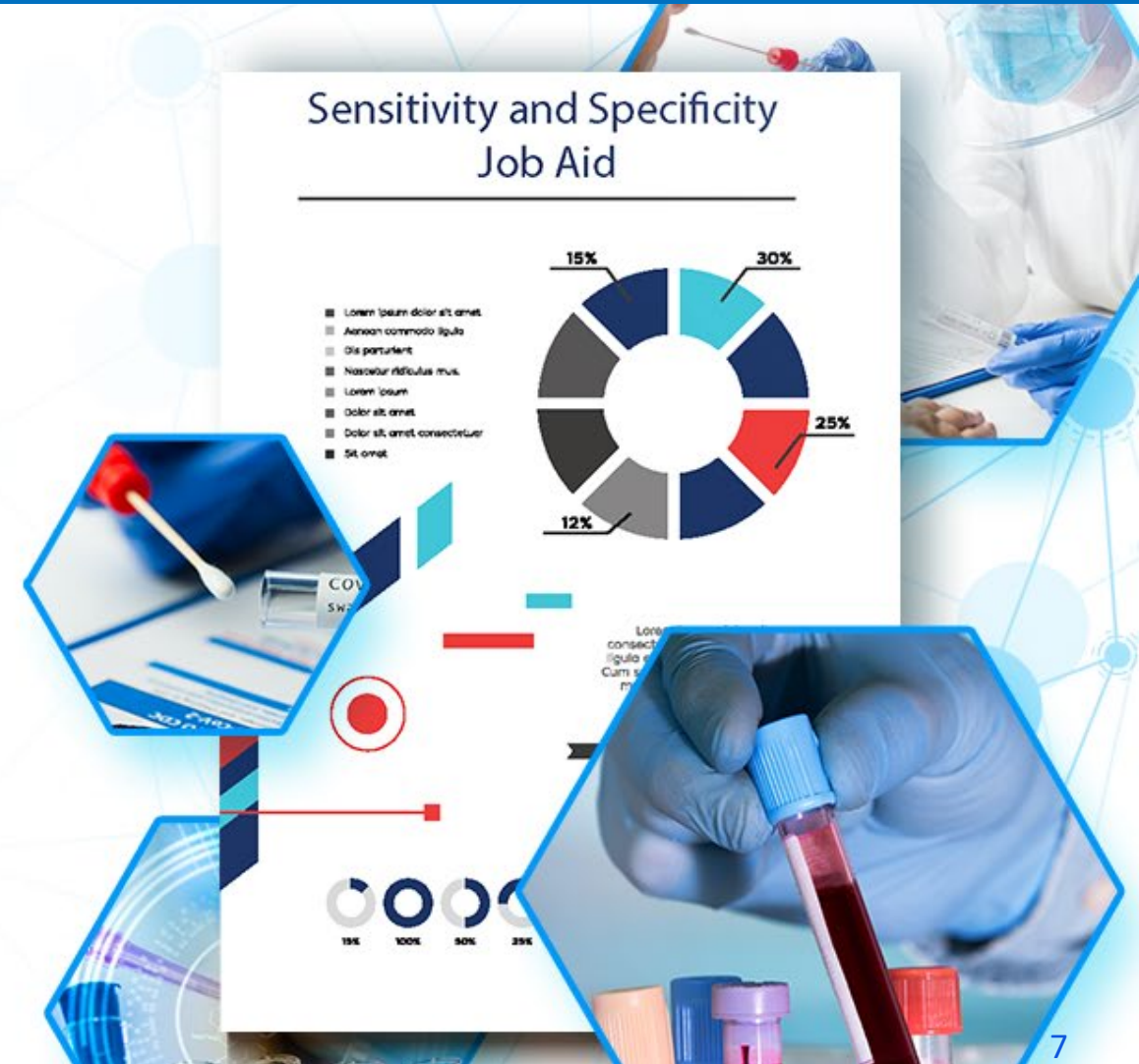


Sensitivity and Specificity Job Aid

Understanding sensitivity and specificity helps determine test selection and whether retesting might be necessary.

OneLab's Sensitivity and Specificity job aid helps public and clinical laboratory professionals understand how specificity and sensitivity performance characteristics affect test result interpretation.

This job aid is available at www.cdc.gov/labtraining/onelab/network.html.



NGS Quality Initiative Introduces Redesigned Page & New Resources

The screenshot shows a web page titled "Laboratory Quality" with a breadcrumb trail: "Laboratory Quality > Molecular Methods > The Next Generation Sequencing Quality Initiative". The page features a left-hand navigation menu with items like "Laboratory Quality", "About Laboratory Quality", "CLIA", "CLIA C", "Molecular Methods", "The Next Generation Sequencing Quality Initiative", "QMS Tools and Resources", "Learn about the Initiative", "New Tools Feature Story", "Meet NGS Quality Initiative Project Partners", "Find Additional NGS Quality Materials", "GeT-RM", and "Tools and Resources".

The main content area is titled "QMS Tools and Resources" and contains the following text:

Public health and clinical laboratories require a foundation of quality to ensure fidelity in the total testing process. Laboratory operations need to be reliable, tests need to be as accurate as possible, and test results must be promptly delivered. Failures at any step within these systems could result in consequences for patient and population health.

Quality Management Systems (QMS) have been described by the International Organization for Standardization (ISO) and the Clinical Laboratory Standards Institute (CLSI) as "coordinated activities to direct and control an organization with regard to quality." A QMS investigates the entire laboratory system, and many accreditation programs now require clinical laboratories to develop and follow QMS for their NGS-based tests.

Use of trade names is for identification only and does not imply endorsement by the US Department of Health and Human Services.

CDC and APHL adopted the CLSI 12 QSEs as building blocks for developing a QMS for clinical and public health laboratories performing NGS-based tests.

Below the text is a "Manufacturer" filter section with a search bar and a list of manufacturers:

- Illumina (33)
- Oxford Nanopore (7)
- ThermoFisher (20)

To the right of the manufacturer list is a "Search for Tools" section with a search input field and a search icon. Below the search field, it says "Found 90 files." and includes "Show 10" and "Order By..." dropdown menus.

At the bottom of the page, there is a "QMS Assessment Tool" section with a document icon and the text: "CDC wants users to know that individuals and organizations who download this Excel spreadsheet for use in their quality management system should consider the accessibility needs of their staff, since this product is not".

<https://www.cdc.gov/labquality/qms-tools-and-resources.html>

Clinical Laboratory COVID-19 Response Calls are now LOCS Calls



We Want to Hear From You!

Training and Workforce Development

Questions about education and training?

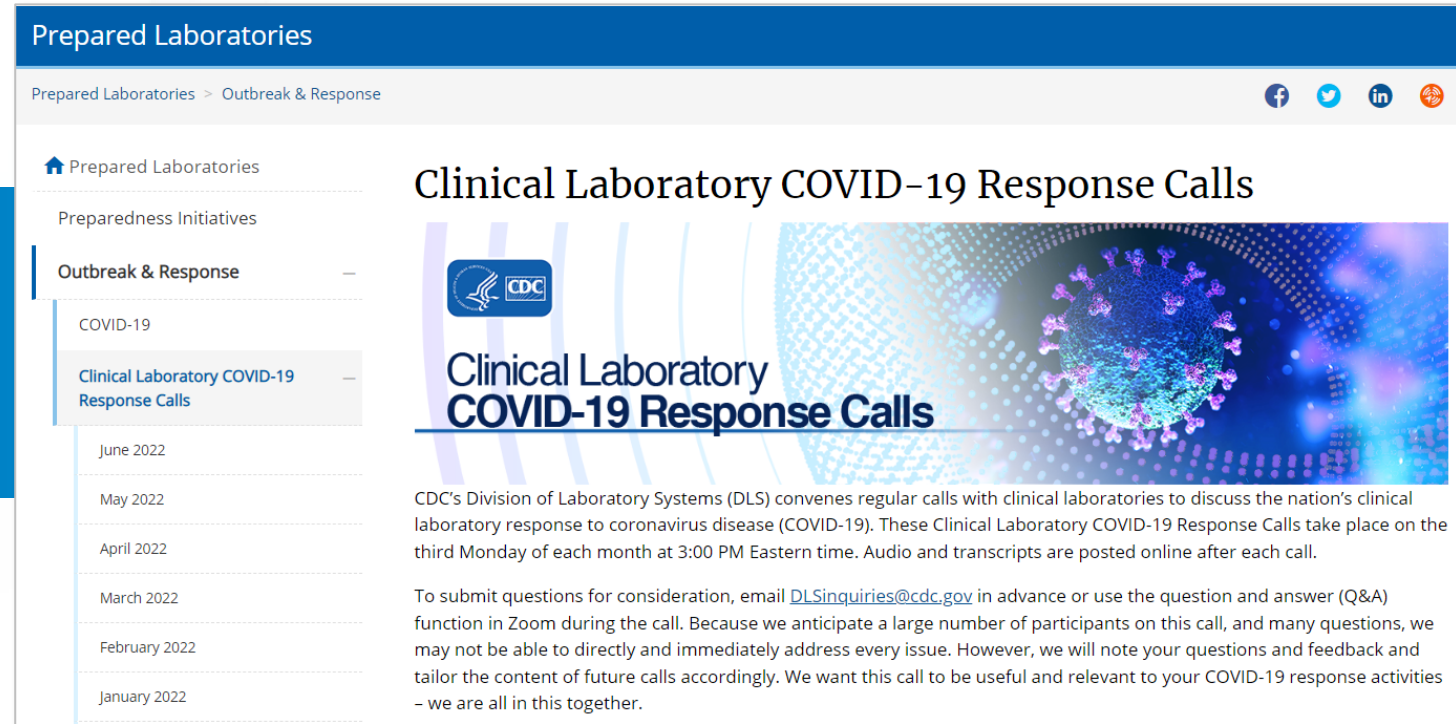
Contact LabTrainingNeeds@cdc.gov



CDC Preparedness Portal

<https://www.cdc.gov/csels/dls/preparedlabs/covid-19-clinical-calls.html>

Find CLCR call information, slides, transcripts, and audio recordings on this page



The screenshot shows the 'Prepared Laboratories' section of the CDC website. The main heading is 'Clinical Laboratory COVID-19 Response Calls'. Below the heading is a CDC logo and a large image of a coronavirus particle. The text describes the purpose of the calls: 'CDC's Division of Laboratory Systems (DLS) convenes regular calls with clinical laboratories to discuss the nation's clinical laboratory response to coronavirus disease (COVID-19). These Clinical Laboratory COVID-19 Response Calls take place on the third Monday of each month at 3:00 PM Eastern time. Audio and transcripts are posted online after each call.' It also provides contact information for submitting questions: 'To submit questions for consideration, email DLSinquiries@cdc.gov in advance or use the question and answer (Q&A) function in Zoom during the call. Because we anticipate a large number of participants on this call, and many questions, we may not be able to directly and immediately address every issue. However, we will note your questions and feedback and tailor the content of future calls accordingly. We want this call to be useful and relevant to your COVID-19 response activities - we are all in this together.'

Prepared Laboratories

Prepared Laboratories > Outbreak & Response

Preparedness Initiatives

Outbreak & Response

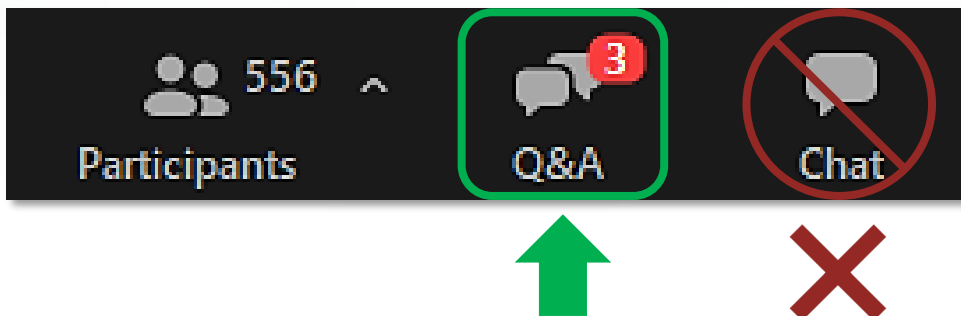
- COVID-19
 - Clinical Laboratory COVID-19 Response Calls
 - June 2022
 - May 2022
 - April 2022
 - March 2022
 - February 2022
 - January 2022

How to Ask a Question

- **Using the Zoom Webinar System**

- Click the **Q&A button** in the Zoom webinar system
- Type your question in the **Q&A box** and submit it
- **Please do not submit a question using the chat button**

- For media questions, please contact CDC Media Relations at media@cdc.gov
- If you are a patient, please direct any questions to your healthcare provider



Division of Laboratory Systems

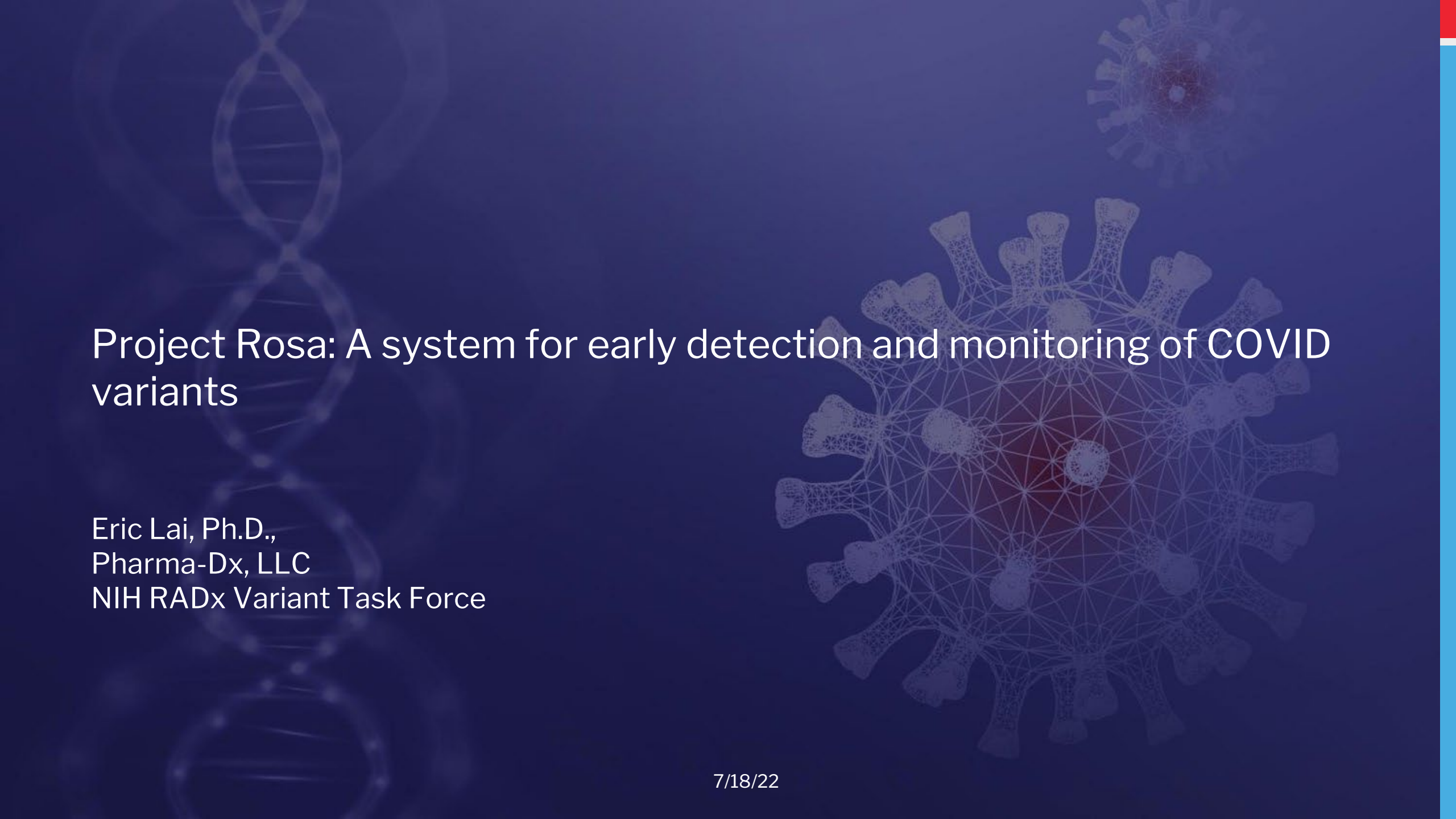
Slide decks may contain presentation material from panelists who are not affiliated with CDC. Presentation content from external panelists may not necessarily reflect CDC's official position on the topic(s) covered.



SARS-CoV-2 Variants Update

Clinton Paden
Division of Viral Diseases, CDC





Project Rosa: A system for early detection and monitoring of COVID variants

Eric Lai, Ph.D.,
Pharma-Dx, LLC
NIH RADx Variant Task Force

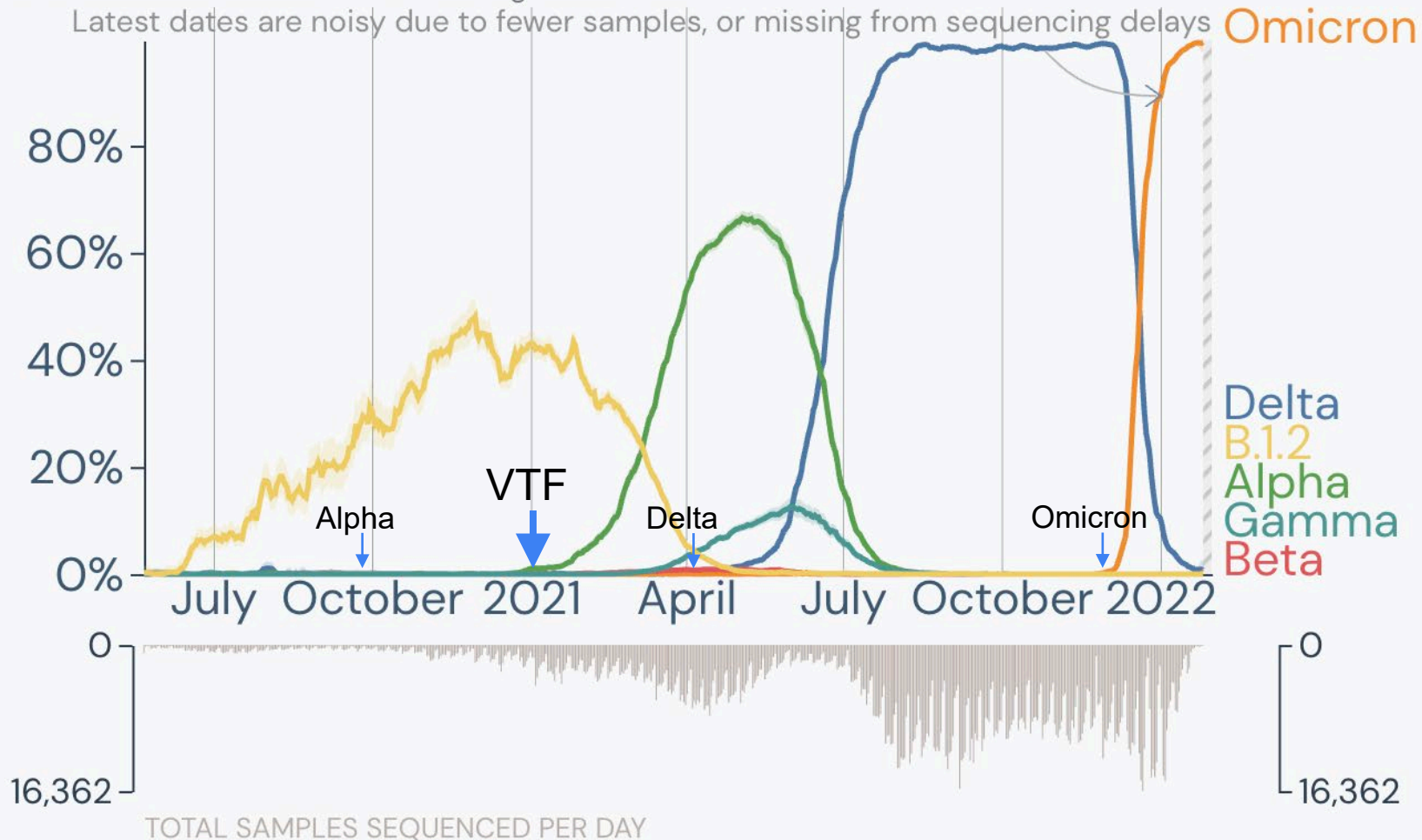
SAR-CoV-2 variant lineage prevalence in the US

Mutation and case prevalence over time in United States show confidence intervals

— 7 day rolling average of percent sequences with mutation(s)

■ 95% confidence interval ▨ missing recent data

Latest dates are noisy due to fewer samples, or missing from sequencing delays



Observations:

- New variants appeared in ex-US countries and migrated to the US
- There is a window of opportunity for the US to prepare for the appearance of new variants
- The duration of first appearance in the US and taking over the variant(s) is getting shorter and shorter

Specific Aims of Project ROSA

- Specific Aim 1. Can we develop a highly sensitive and specific assay that can detect all positive COVID samples and is not sensitive to variants?
 - All current COVID tests were designed using the original Wuhan COVID strain and have the potential of “missing/not detecting” new COVID variants. A lot of efforts are spent in determining whether any specific assay can detect all variants.
- Specific Aim 2. Can we develop a system to potentially identify new variant and to monitor known variants in a cost and time efficient manner to complement the CDC sequencing effort?
 - Variants are detected and monitored by random sequencing (i.e surveillance sequencing up to 5%) of positive COVID samples. The process is labor intensive (i.e. picking of positive samples) and the procedure is time consuming (weeks) and expensive (hundred of \$\$) per sample.

Specific Aim 1: Develop a highly sensitive and specific variant agnostic assay

In collaboration with CDC and ThermoFisher, we have identified specific markers for the detection of most (>99%) COVID samples independent of variant lineage. S:D614G (VTF), N:SC2 region (CDC) and ORF1ab (ThermoFisher). The positivity rates have been confirmed bioinformatically and experimentally.

		Variant Agnostic Marker			Positive Calls	PPA (%)
		S:D614G	nsp10 gene	N gene SC2		
Number of Markers	3	+	+	+	1,024	99.3
	2	+	+		1,020	98.9
		+		+	1,021	99
	1		+	+	1,023	99.2
		+			993	96.3
				+	1,018	98.7
0				990	96	
Total SARS-CoV-2 positive samples					1,031	

Testing of 1,024 COVID samples including Alpha, Beta, Gamma, Delta, Epsilon, Eta, Iota, Kappa, Lambda, Mu

Specific Aim 2: Use of a panel of SNP markers/mutations to identify known PANGO variant VOC/I lineage

Nucleotide Mutations	AA Mutation	Marker Set					Classification Outcome
		48	24	16	12	8	
nsp10 gene (position 13025-13441)	None	+	+	+	+	+	SARS-CoV-2 detected
A23403G	S:D614G	+	+	+	+		
N gene SC2 (position 29461-29482)	None	+					
T16176C	None	+	+	+	+	+	Alpha
A21801C	S:D80A	+	+	+	+	+	Beta
A22812C	S:K417T	+	+	+	+	+	Gamma
C21618G	S:T19R	+	+	+	+	+	Delta
C22995A	S:T478K	+	+	+	+	+	Delta
T7424G	orf1ab:F2387V	+	+	+	+	+	Lambda
A13057T	None	+	+	+	+	+	Mu
G22018T	S:W152C	+	+	+	+		Epsilon
A16500C	orf1b:Q1011H	+	+	+	+		Iota
T22917A	S:L452Q	+	+	+	+		Lambda
A11456G	orf1ab:I3731V	+	+	+			Delta
A28699G	None	+	+	+			Eta
G23593C	S:Q677H	+	+	+			Eta
A24775T	S:Q1071H	+	+	+			Kappa
TACATG21765-----	S:HV69--	+	+				Alpha
TTA21991---	S:Y144-	+	+				Alpha (when combined with T16176C)
CTTTACTTG22281-----	S:LLA241--	+	+				Beta (when combined with A21801C)
T733C	None	+	+				Gamma
T22917G	S:L452R	+	+				Delta (or Epsilon when combined with G22018T)
A22320G	S:D253G	+	+				Iota (when combined with A16500C)
G23012C	S:E484Q	+	+				Kappa (when combined with A24775T)
C27925A	ORF8:T11K	+	+				Mu
G22132T	S:R190S	+					Gamma
C23604G	S:P681R	+					Delta
C25469T	ORF3a:S26L	+					Delta

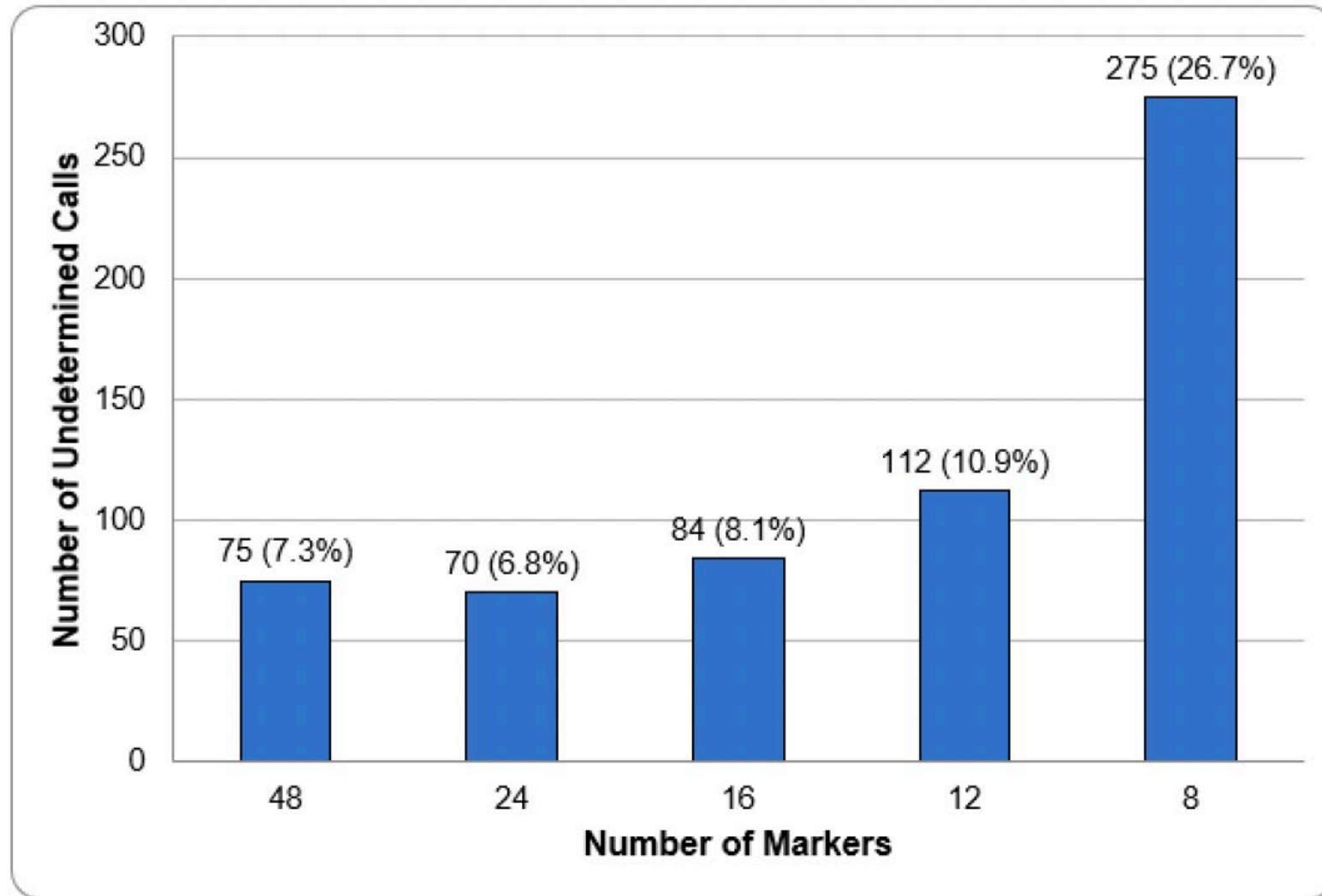
Analytical performance of the variant specific panels

	48 Markers		24 Markers		16 Markers		12 Markers		8 Markers	
	PPA (%)	NPA (%)	PPA (%)	NPA (%)	PPA (%)	NPA (%)	PPA (%)	NPA (%)	PPA (%)	NPA (%)
Alpha	99.2	99.2	99.2	99.2	98.4	99.1	98.4	99.1	98.4	99.1
Beta	100	100	100	100	100	100	100	100	100	100
Gamma	100	100	100	100	100	100	100	100	100	100
Delta	98.9	99.8	98.7	99.6	98.7	99.6	98.7	99.6	98.9	99.8
Epsilon	96.3	99.7	96.3	99.7	96.3	99.7	96.3	99.7	*	91.5
Eta	100	100	100	100	100	100	*	97.3	*	97.3
Iota	100	99.9	100	99.9	100	99.9	100	99.9	*	91.3
Kappa	100	100	100	100	100	100	*	99.9	*	99.9
Lambda	100	100	100	100	100	100	100	100	100	100
Mu	100	100	100	100	100	100	100	100	100	100

*Cannot call

Genotyping of 1,024 COVID samples including Alpha, Beta, Gamma, Delta, Epsilon, Eta, Iota, Kappa, Lambda, Mu

Number of “undetermined” calls

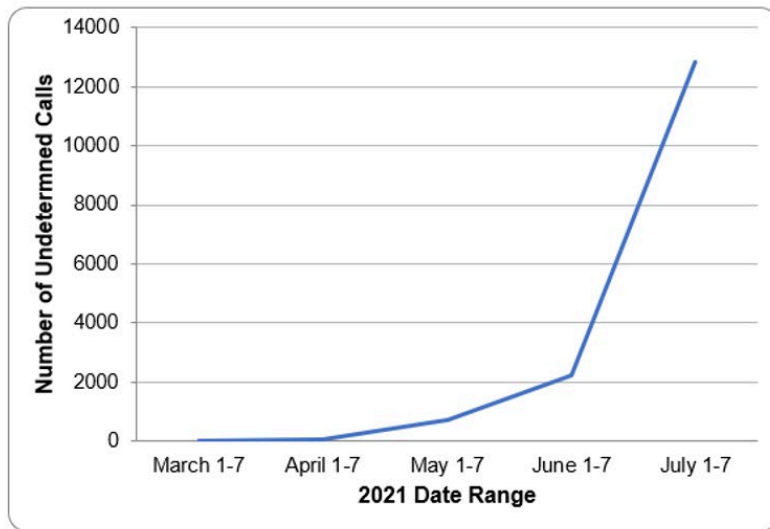


What would we have seen if we had ROSA before Delta appeared in the US?

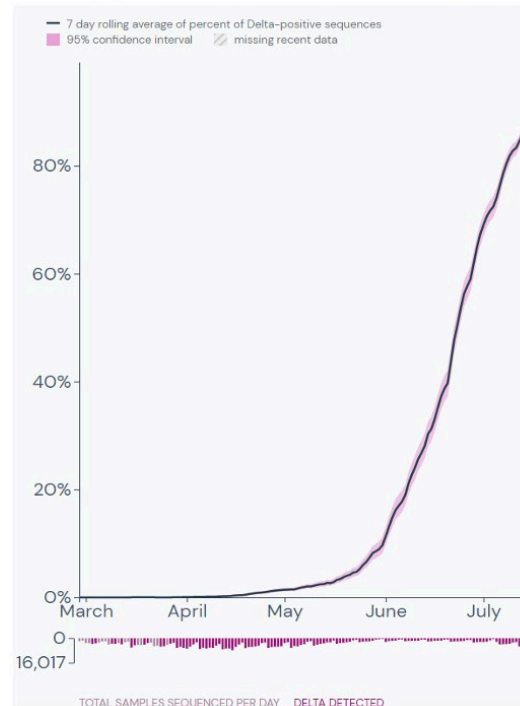
Here are the steps taken to evaluate how ROSA would have worked for Delta:

- Remove from the 12 markers classifier config file any mutation linked to Delta resulting in a list of 10 markers including the 2 positivity ones.
- Run the simulation using as data the first week of each month in GISAID for **North America from November 2020 to July 2021**.

of undetermined samples using 10 markers (without Delta)



Appearance of Delta in the US



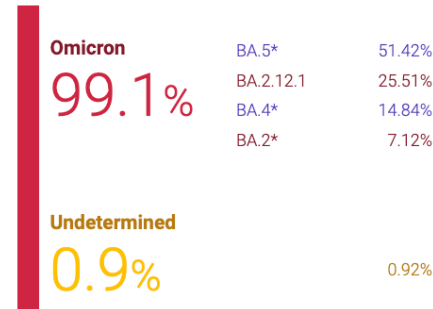
With no prior knowledge of Delta, the ROSA classifier would have categorized 99.93 % of Delta sequences as “Undetermined” and therefore recommended for sequencing

ROSA Tracker: <https://tracker.rosalind.bio/dashboard>

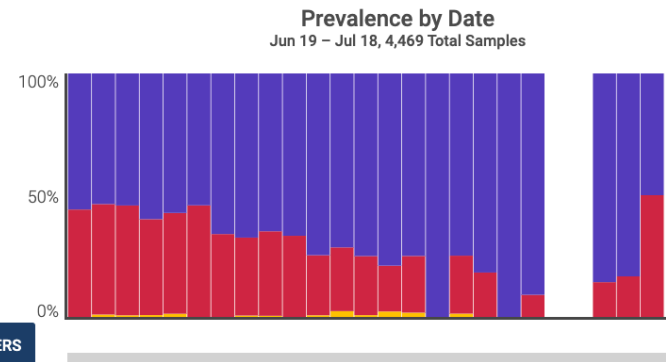
Genotyping

Genotyping Prevalence over Time

Enabled by data from contributing labs: UW Medicine, Helix, Aegis Sciences Corporation, Ovation
Last updated Jul 15, 2022



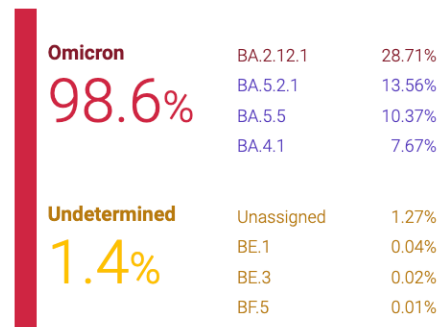
[VIEW LINEAGES](#) [VIEW MARKERS](#)



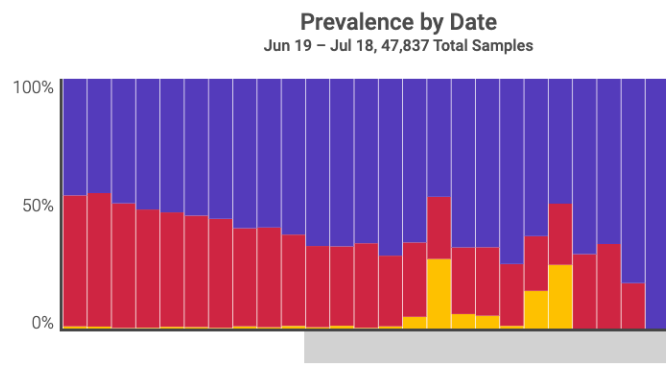
Sequencing

Sequencing Prevalence over Time

Enabled by data from **GISAID**
Last updated Jul 18, 2022



[VIEW LINEAGES](#)



*Noise due to delays in da

Reference: Lai E, et al., A Method for Variant Agnostic Detection of SARS-CoV-2, Rapid Monitoring of Circulating Variants, and Early Detection of Emergent Variants Such as Omicron. J Clin Microbiol. 2022 Jun 29:e0034222. doi: 10.1128/jcm.00342-22. Epub ahead of print. PMID: 35766514.

Value proposition – NGS Surveillance vs Project Rosa

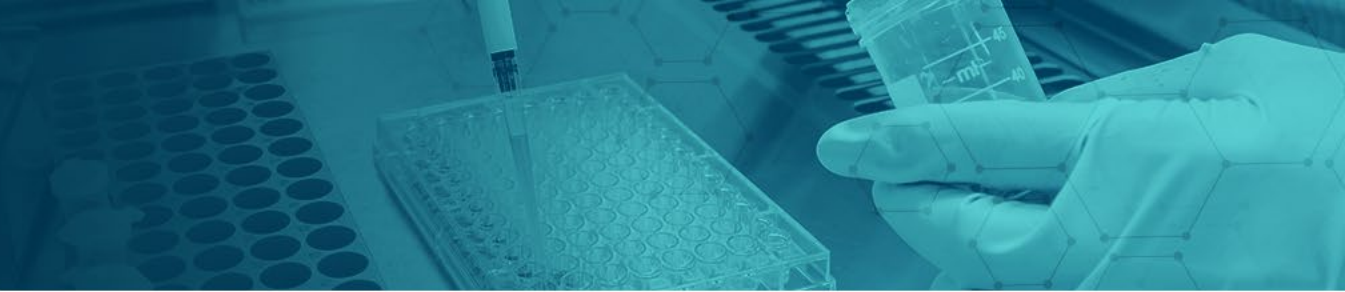
Metrics	Project Rosa	Next Generation Sequencing (NGS)	Project Rosa Compared to NGS
Cap-Ex Cost (List Price) per set	\$125K	\$850K-\$1M	5x-8x Lower Cost
Cost Per Sample	\$50	\$125-\$500	5x-20x Lower Cost
Turn-Around Time	<5 hours	7 - 10 Days	Up to 30x Faster
Number of Technicians Required	1 FTE	2-3 FTE	2x Less Labor Required
Lab Resource Proficiency	Standard PCR Experience	High-End Bio-Informatics	
Sample coverage	~100% of COVID samples	5% of random positive samples	20x increase in coverage

Proposal: Use of genotyping to monitor known variants and focus the use of NGS for detection of new variants

Wide spread adaption plan and long-term implementation plan

- FDA: discussion on approval path for the genotyping assay
- CDC: collaborative path for CLIA lab adaption
- CMS: discussion on reimbursement/pricing model(s)
- Long Term Implementation:
 - Informatic automated monitoring of new variants
 - Proactive monitoring of the variants prevalence globally and in the US
 - Monitoring of the rate of increase in prevalence
 - Monitoring of US regional prevalence
 - Predictive modelling of biological significance mutation(s)
 - Establish an expert panel to review marker panel composition and update marker panel at a regular basis (similar to Flu vaccine committee).

Division of Laboratory Systems



FDA Update

Tim Stenzel

US Food and Drug Administration (FDA)



U.S. Food and Drug Administration

- **COVID-19 Emergency Use Authorization (EUA) Information for Medical Devices**
<https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices>
- **COVID-19 In Vitro Diagnostic EUAs**
<https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas>
- **COVID-19 Frequently Asked Questions**
<https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions>
- **COVID-19 Updates**
<https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#2019-ncov>
- **FDA Townhall Meetings**
<https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/virtual-town-hall-series-immediately-effect-guidance-coronavirus-covid-19-diagnostic-tests-06032020>
- **Independent Evaluations of COVID-19 Serological Tests**
<https://open.fda.gov/apis/device/covid19serology/>

U.S. Food and Drug Administration

- **COVID-19 Diagnostic Development**

CDRH-EUA-Templates@fda.hhs.gov

- **Spot Shortages of Testing Supplies: 24-Hour Support Available**

1. Call 1-888-INFO-FDA (1-888-463-6332)
2. Then press star (*)

- **FDA MedWatch**

<https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program>

Division of Laboratory Systems

Monkeypox Update

Christina Hutson
Monkeypox Response, CDC



Division of Laboratory Systems

These slides were shared during the call but are not available for public distribution.



Next Scheduled Call

The next call will be on

Monday, August 15 @ 3:00 PM to 4:00 PM ET



CDC Social Media

<https://www.facebook.com/CDC>



<https://twitter.com/cdcgov>

<https://www.instagram.com/cdcgov>



<https://www.linkedin.com/company/cdc>

Thank You For Your Time!

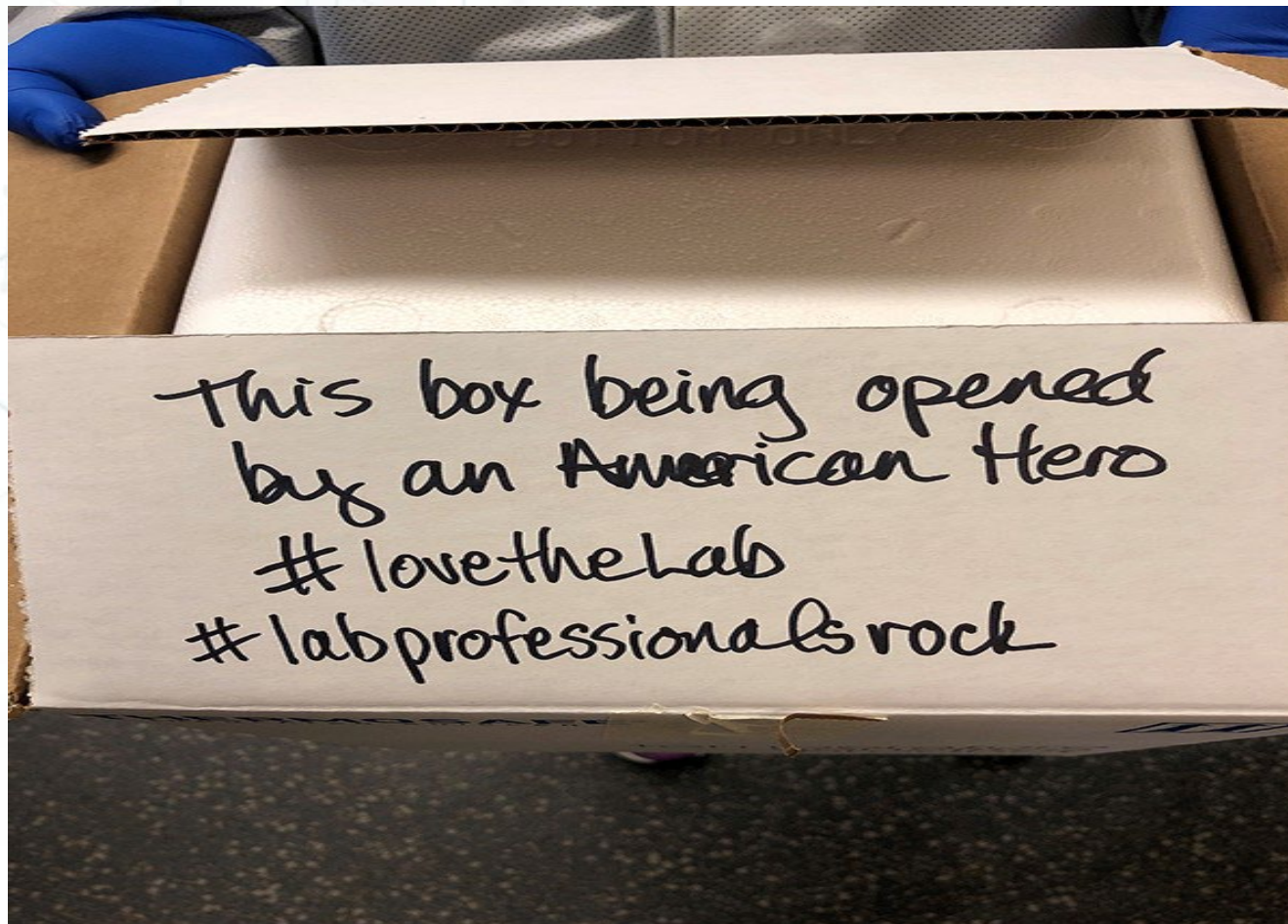


Photo submitted by the Microbiology Laboratory at The University of Pittsburgh Medical Center



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of Centers for Disease Control and Prevention.