Clinical Laboratory COVID-19 Response Call

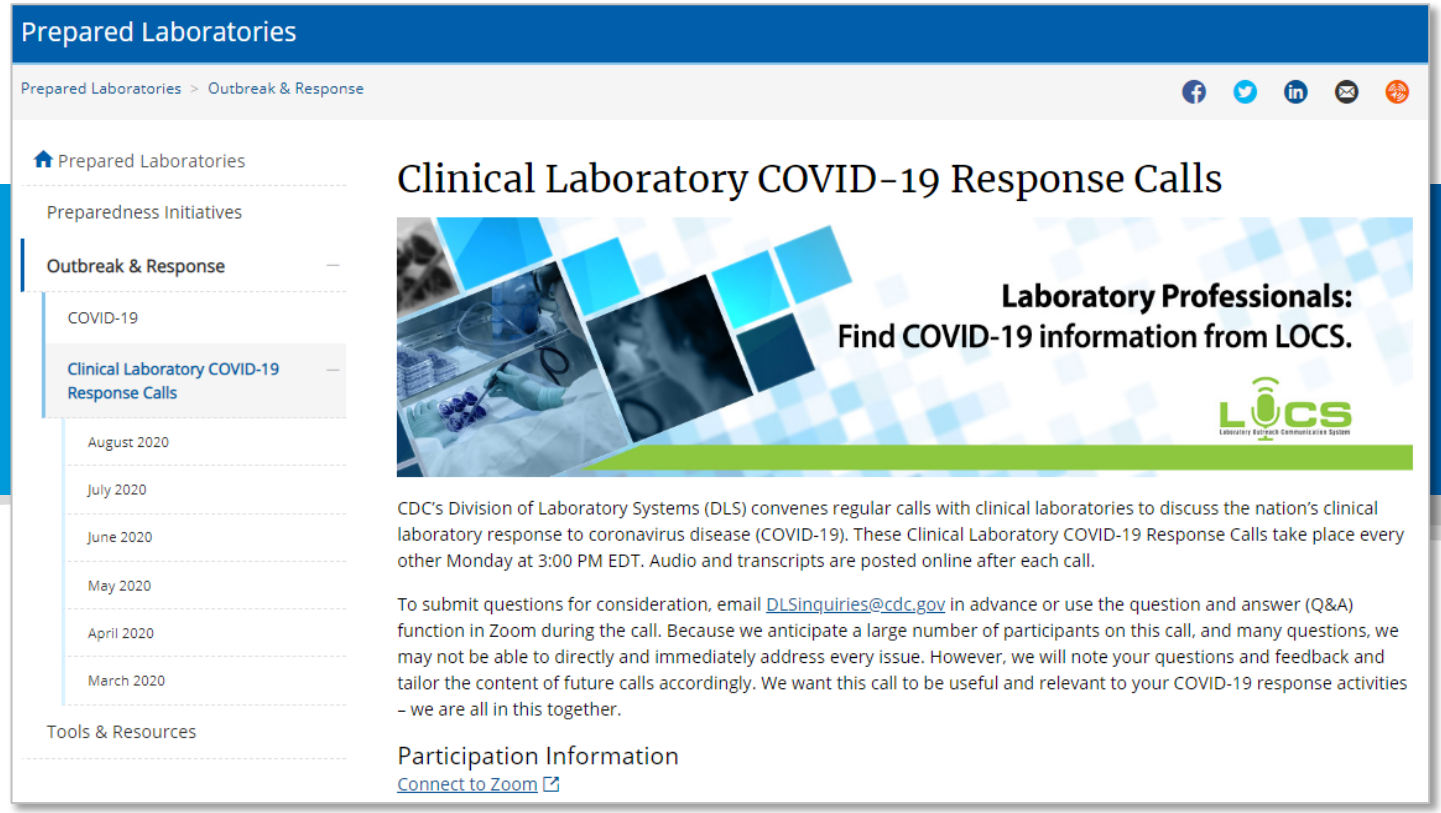
Monday, July 26, 2021, at 3:00 PM EDT

- **Welcome**
  - Nancy Anderson, CDC Division of Laboratory Systems (DLS)
- **CDC Influenza SARS-CoV-2 Multiplex Assay**
  - Brandi Limbago, CDC Laboratory and Testing Task Force for the COVID-19 Response
- **Genomic Changes Causing SARS-CoV-2 Detection Partial Failure**
  - Daniel D. Rhoads, Cleveland Clinic
- **FDA Update**
  - Tim Stenzel, U.S. Food and Drug Administration (FDA)

CDC Preparedness Portal

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

Find CLCR call information, transcripts, and audio recordings on the CDC Preparedness Portal



Schedule for Clinical Laboratory COVID-19 Response Calls

The next call will be on **Monday, August 9** from

3:00 PM to 4:00 PM EDT

We Want to Hear from You!

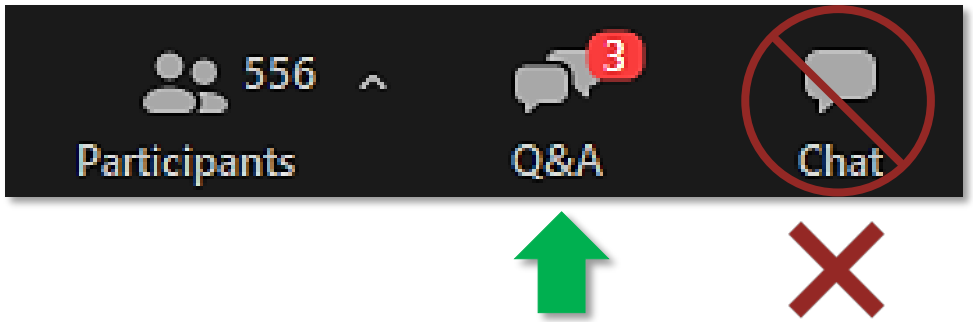
Training and Workforce Development

Questions about education and training?

Contact LabTrainingNeeds@cdc.gov

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

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.

CDC Influenza SARS-CoV-2 Multiplex Assay

Brandi Limbago
CDC Laboratory and Testing Task Force for the COVID-19 Response

Genomic changes causing SARS-CoV-2 detection partial failure

CDC’s Clinical Laboratory COVID-19 Response Call

26 July 2021

Daniel D. Rhoads, MD, FCAP, D(ABMM)

Section Head of Microbiology

Cleveland, Ohio

Cleveland Clinic

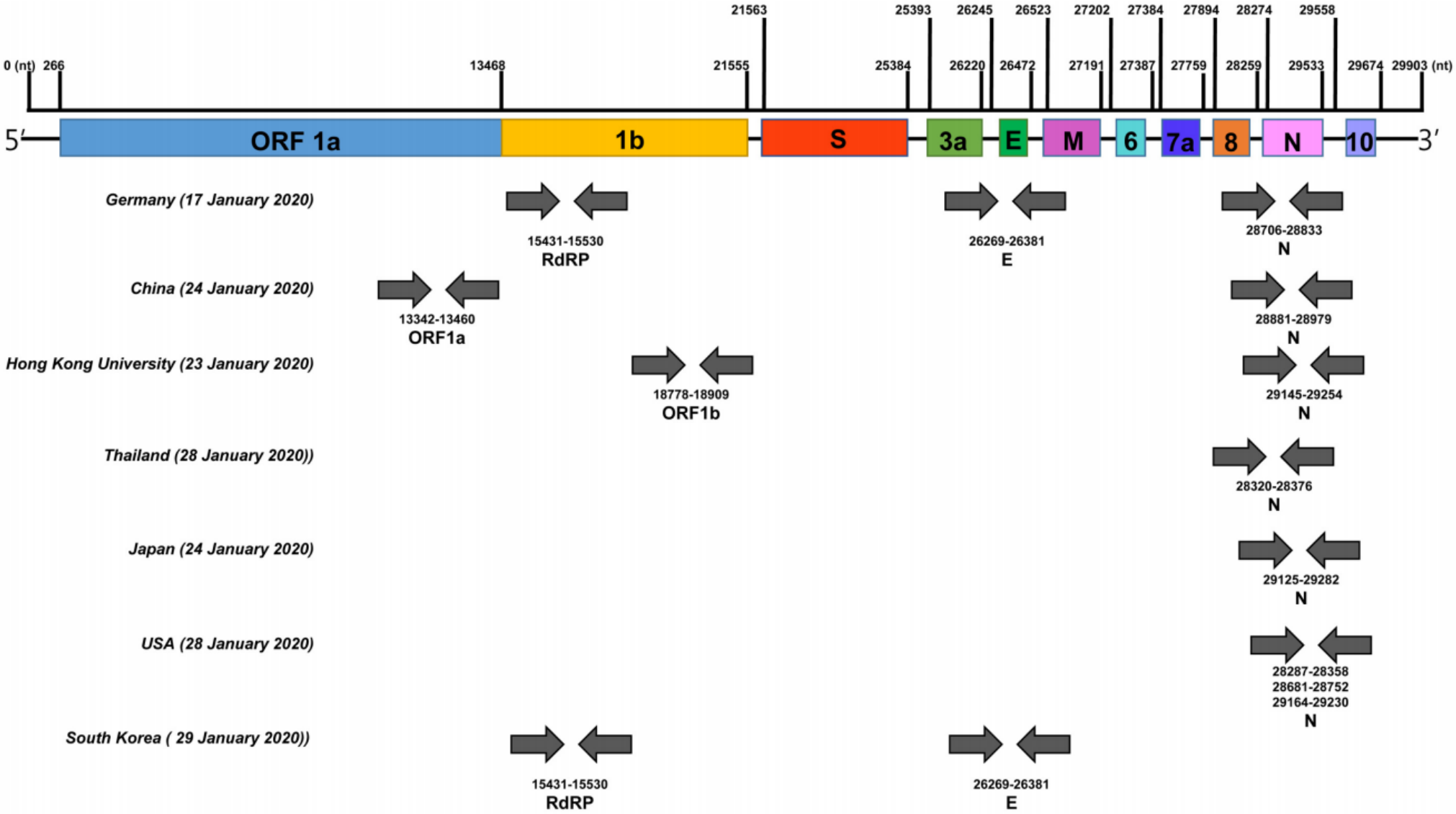


Fig. 5. A representative diagram showing currently available diagnostic primer sets on SARS-CoV-2 genome.
Numbers represent genome positions according to SARS-CoV-2 isolate Wuhan-Hu-1 (GenBank: MN908947.3). Each primer set for the diagnosis was indicated by grey arrows.

Ahn *et al.* doi: 10.4014/jmb.2003.03011

Variant of Concern

Variant of Concern

A variant for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures.

Possible attributes of a variant of concern:

In addition to the possible attributes of a variant of interest

- Evidence of impact on diagnostics, treatments, or vaccines
  - Widespread interference with diagnostic test targets […]

https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

SARS-CoV-2 detection failure

- To my knowledge, no complete diagnostic failures have been reported to date.
- Several “partial” failures or single target failures have been reported and will be described.

Know your assay(s)

- Some *in vitro* diagnostic (IVD) assays use a single genomic target to detect SARS-CoV-2. Single mutations could result in complete diagnostic failure.
- Many IVD assays use multiple genomic targets to detect SARS-CoV-2, which would require multiple mutations to achieve complete diagnostic failure.
  - Some assays use different fluorophores for each of multiple targets. Single target failure can be identified.
  - Some assays use a single fluorophore for multiple targets, which helps to facilitate multiplexing. Single target failure cannot be identified.

Finding failures: Case 1

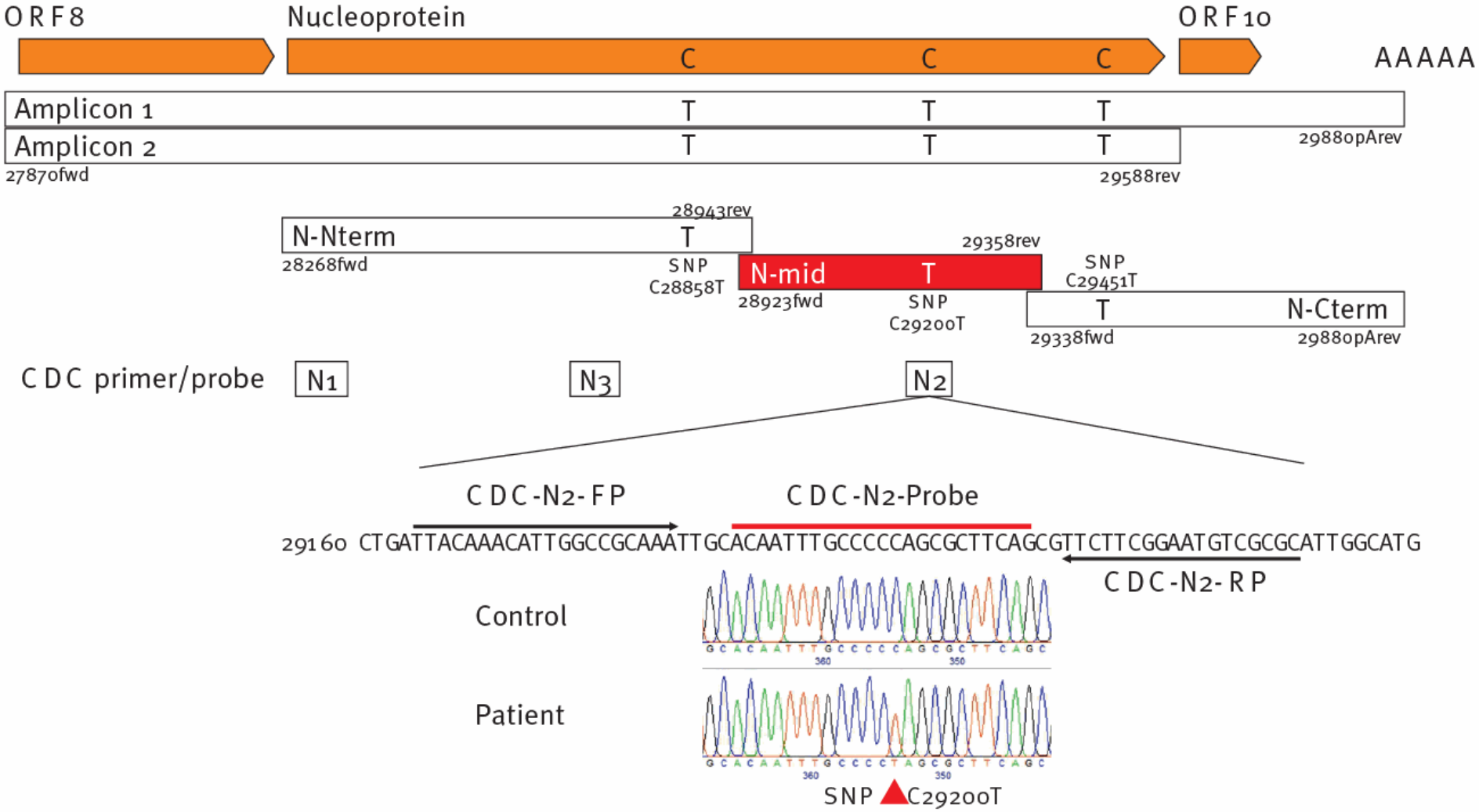
Finding failures: Case 1

One of two targets detected raised curiosity.

“Since information on the proprietary […] primers and probe(s) was unavailable […].”

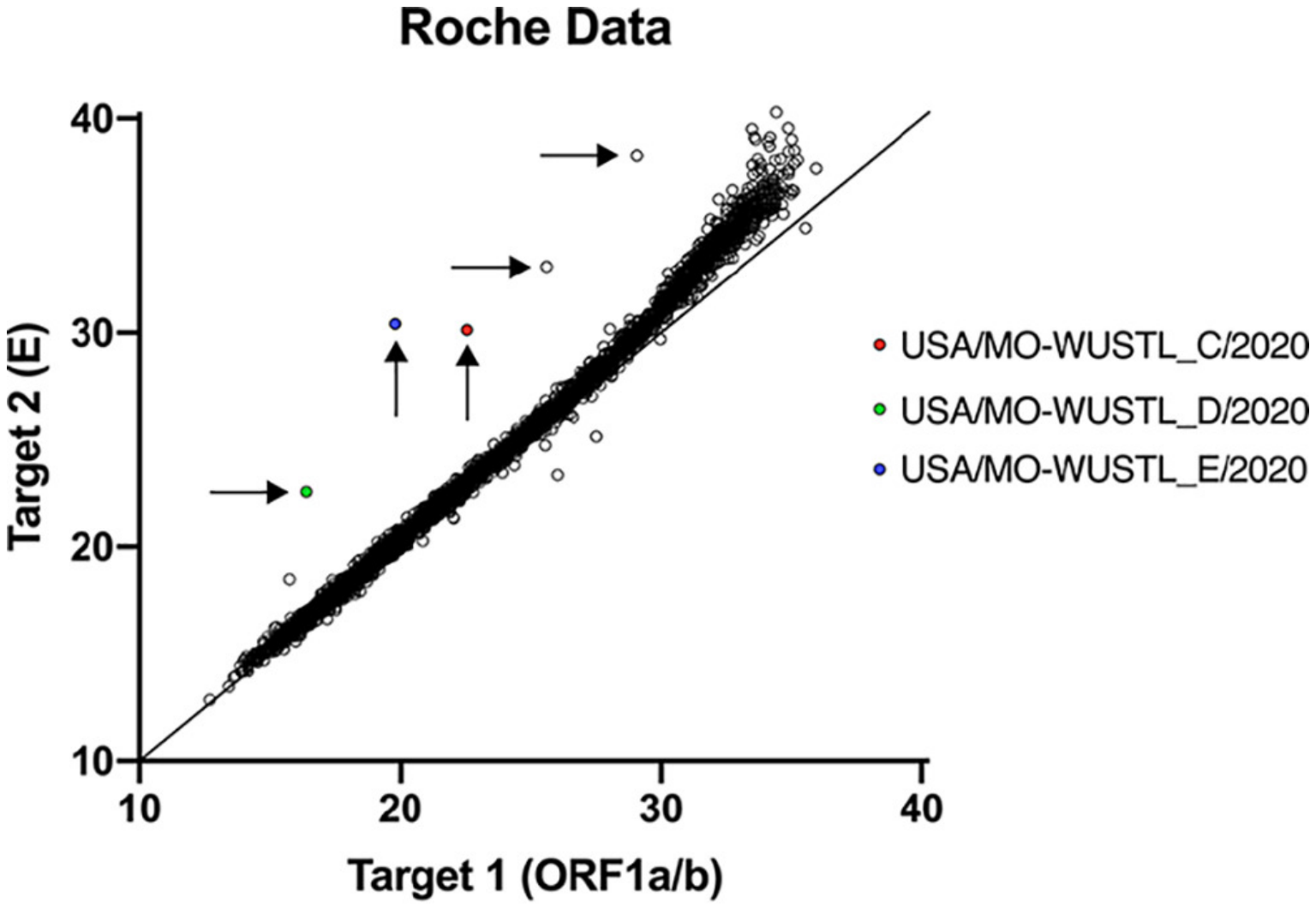
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.39.2001650

Finding failures: Case 1



https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.39.2001650

Finding failures: Case 2



https://journals.asm.org/doi/10.1128/JCM.00075-21

Empiric detection failures of commercial assays

Polymorphism	Target Failure	Gene	Mutation	Associated Lineage	Assay	Reference
g.21765_21770 deletion	Complete	Spike	2 AA Deletion	B.1.1.7 (Alpha)	Thermo Fisher TaqPath	https://doi.org/10.2807/1560-7917.ES.2021.26.3.2100008
g.29197C>T	Complete or Partial	Nucleocapsid	Synonymous	B.1.1.222, B.1.1.519	Cepheid Xpert	https://doi.org/10.1128/JCM.00913-21
g.29200C>W	Complete or Partial	Nucleocapsid	Synonymous		Cepheid Xpert	https://journals.asm.org/doi/10.1128/JCM.03278-20 ; https://doi.org/10.2807/1560-7917.ES.2020.25.39.2001650
g.26340C>T	Complete	Envelope	Synonymous		Roche cobas 6800/8800	https://doi.org/10.1128/JCM.01598-20
g.26372G>T	Partial	Non-coding (E region)	N/A		Roche cobas 6800/8800	https://doi.org/10.1128/JCM.00075-21

Surveillance sequencing is helpful

- Currently, once a polymorphism has empirically been demonstrated to result in target failure, then sequencing surveillance data can be used to monitor the frequency of the mutation.

- In the future, ideally genomic regions targeted by IVDs would be made publicly available by manufacturers, so prospective investigation of polymorphisms occurring within targeted regions could be identified. Then, the sentinel laboratory performing the sequencing could subsequently empirically challenge the IVD assay known to target the polymorphic region.

References

Vogels, C.B.F., Brito, A.F., Wyllie, A.L. et al. Analytical sensitivity and efficiency comparisons of SARS-CoV-2 RT–qPCR primer–probe sets. Nat Microbiol 5, 1299–1305 (2020). https://doi.org/10.1038/s41564-020-0761-6. https://doi.org/10.1038/s41564-020-0761-6

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Hasan MR, Sundararaju S, Manickam C, Mirza F, Al-Hail H, Lorenz S, Tang P. A Novel Point Mutation in the N Gene of SARS-CoV-2 May Affect the Detection of the Virus by Reverse Transcription-Quantitative PCR. J Clin Microbiol. 2021 Mar 19;59(4):e03278-20. https://journals.asm.org/doi/10.1128/JCM.03278-20

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Cleveland Clinic

Every life deserves world class care.

FDA Update

Tim Stenzel
U.S. Food and Drug Administration (FDA)

U.S. Food and Drug Administration (FDA)

- **COVID-19 Emergency Use Authorization (EUA) Information for Medical Devices**
  https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations
- **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/coronavirus-disease-2019-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/

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration (FDA)

- **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

U.S. FOOD & DRUG ADMINISTRATION

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Thank You For Your Time!

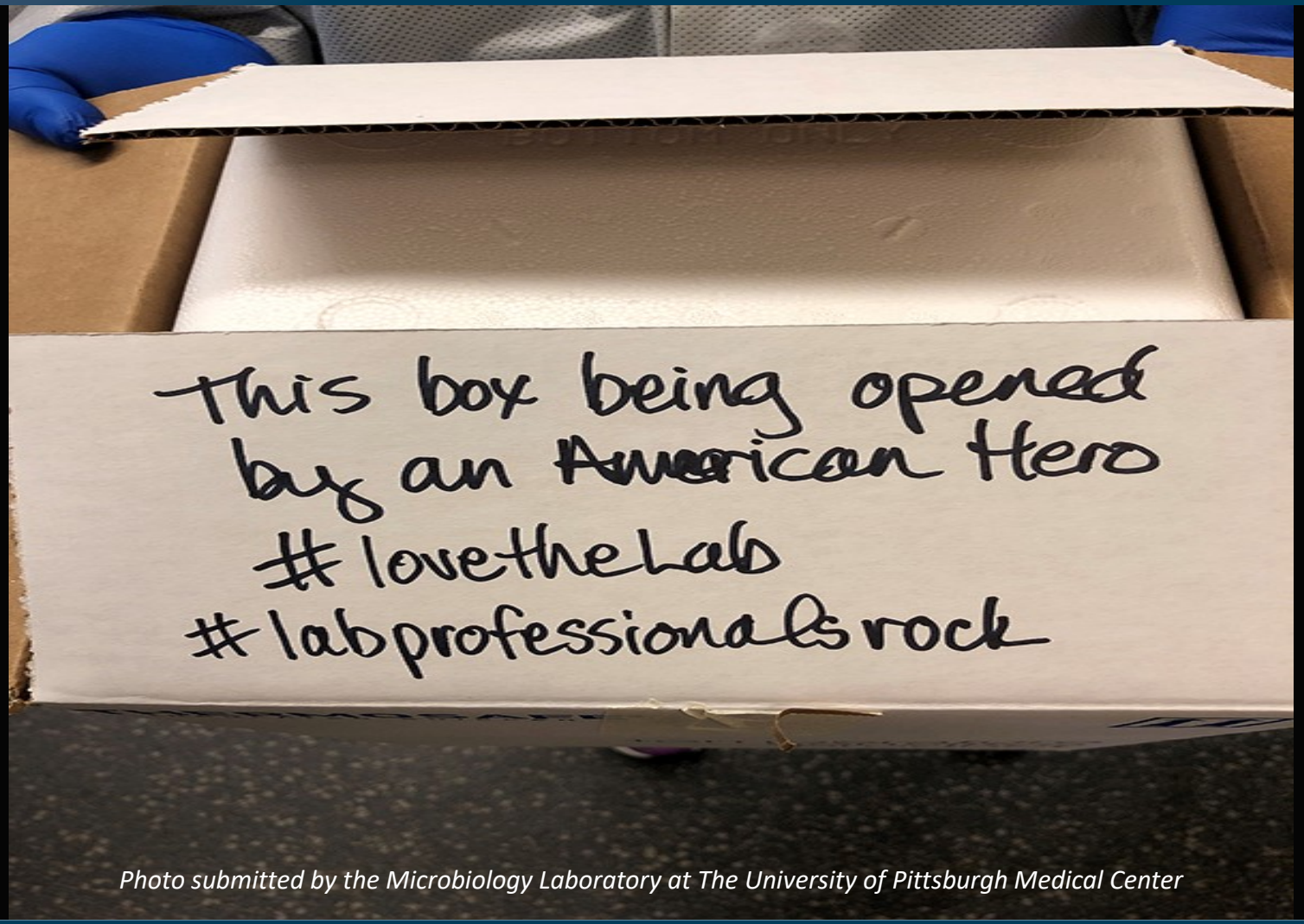

Photo submitted by the Microbiology Laboratory at The University of Pittsburgh Medical Center