CDPH Branch Laboratory
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STATE: CPH889339
CLIA: 05D2197416

**Response to PUBLIC HEALTH LABORATORY STATE INSPECTION – Routine Inspection**
**CONDITION REMAINS – Additional Information Required**

**D3027** - Retention Requirements

The allegation of compliance is not credible, and the evidence of correction is not acceptable.

In its submission, the laboratory stated in the monitoring mechanism:

> "Monthly audits for FY 2021 to determine availability and compliance with all required elements are performed by the quality organization. The availability of the requisition and report was confirmed for 10 samples via a routine tracer audit performed 02/26/2021. An audit of an additional 25 samples was initiated 03/11/2021 to verify that requisitions are available and include all necessary requisition elements."

To correct this deficiency, the laboratory must

- During the on-site follow-up inspection on March 18, 2021, the laboratory was able to provide the audit performed on February 26, 2021.
- Provide the March 11, 2021, audit of 25 additional samples mentioned in the allegation of compliance.

***--------- Response Start ---------***

Reference attachment Attachment D3027_1_21Audit008_End-To-End Tracer – Final Report with Requisitions.pdf for the March 18, 2021 audit showing sample retention.

**(1) Immediate Corrective Action:** Through cooperation with Color Genomics and the CDPH Branch Laboratory, a method to present the data from the electronic order in the form of a requisition was established. The Laboratory Director and member of the Quality Assurance team received training that allows them to effectively and efficiently access the electronic requisitions and reports stored by Color Genomics, on demand.

**(2) Patient Impact:** Per Lab Director Dr. Rosendorff, since the requisitions and reports have been maintained there is no impact on patient care.

**(3) Preventative Measure:** Through the use of CA-PER-FM-031, Pre/Post Analytical QA Training Checklist, the lab will continue to ensure the quality assurance and laboratory director staff at the CDPH Branch Laboratory has access to the Color Genomics system and can effectively and efficiently access the data stored by Color Genomics, on demand.

**(4) Monitoring Mechanism:** Monthly audits for FY 2021 to determine availability and compliance with all required elements are performed by the quality organization. The availability of the requisition was confirmed for 10 samples and 25 via a routine tracer audit performed 26Feb2021 and 11MAR2021, respectively, to verify that requisitions are available and include all necessary requisition elements.

*--------- Response End ---------*

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**Response to PUBLIC HEALTH LABORATORY STATE INSPECTION – Routine Inspection**
**CONDITION REMAINS – Additional Information Required**

**D5301** – Test Request

The allegation of compliance is not credible, and the evidence of correction is not acceptable.

In its submission, the laboratory stated in the immediate corrective action:

"Through cooperation with Color Genomics and the CDPH Branch Laboratory, a method to present the data from the electronic order in the form of a requisition was established. The Laboratory Director and the member of the Quality Assurance team received training that allows them to effectively and efficiently access the electronic requisitions and reports stored by Color Genomics, on demand."

To correct this deficiency, the laboratory must

- Identify the quality assurance team who received the training that allows them to effectively and efficiently access the electronic requisitions and reports stored by Color Genomics.
- Provide the training records.

***--------- Response Start ---------***

Color Genomics provided specific training for the five quality assurance team members (Please see Attachment D5301_1_CA_PER_FM_031) for both (1) quality assurance metrics and (2) access to patient PHI data in the form of the electronic requisition and result report. Those that participated in the training are included in the Attachment D5301_2_Training Record_COLOR Dashboard Records_Quality_04Mar2021 training roster.

**(1) Immediate Corrective Action:** The CDPH Branch Laboratory provided the training records for the current quality assurance team members (both the specific training on COLOR software and the additional individual QA proficiency assessments).

**(2) Patient Impact:** As mentioned in finding D3027 of the *CDPH Branch Lab-Routine Inspection_Condition_08-17-2021.pdf* document the CDPH Branch Laboratory was able to provide the audit performed on February 26, 2021. This audit included patient requisitions collected from the Color system. Per Lab Director, Dr. Rosendorff, there is no change in diagnosis, treatment, or recommended patient action (retesting), and there would not be patient harm.

**(3) Preventative Measure:** Through the use of the CA-PER-FM-031, Pre/Post Analytical QA Training Checklist, the lab will continue to ensure that current and future quality assurance staff and laboratory director(s) at CDPH Branch Lab have the knowledge and training to monitor, and produce when requested, a patient requisition from the Color Genomics database.

**(4) Monitoring Mechanism:** Monthly end to end tracer audits for FY 2021 include the availability and compliance with all required elements of the electronic requisition per 42 CFR § 493.1241 along with the ability to provide a hard copy of the requisition on request.

***--------- Response End ---------***

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**Response to PUBLIC HEALTH LABORATORY STATE INSPECTION – Routine Inspection**
**CONDITION REMAINS – Additional Information Required**

**D5423** Establishment of Performance Specifications
CFR 493.1253(b)(2) states

(2) Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:
(i) Accuracy.
(ii) Precision.
(iii) Analytical sensitivity.
(iv) Analytical specificity to include interfering substances.
(v) Reportable range of test results for the test system.
(vi) Reference intervals (normal values).
(vii) Any other performance characteristic required for test performance.

***--------- Response Start ---------***

**(1) Immediate Corrective Action:** The laboratory established test performance specifications and other performance characteristics (LDT Validation) required for test performance on October 24th and obtained LFS approval on the same day prior to the laboratory opening on November 1, 2020 and reporting patient test results. During the validation phase of Oct 19-24th all experiments required by LFS were completed and submitted to LFS for approval. The CDPH laboratory director and LFS approved the LDT validation on October 24, 2020 prior to opening of the laboratory on November 1, 2020. The approved LDT validation included accuracy, precision, analytical sensitivity. Via a Right to Reference letter (See Attachment D5400_9_Right to Reference Letter), the analytical specificity including interfering substances leveraged the EUA data (See Attachments D5400_6 Analytical Study and Attachment D5400_7 8 Performance Evaluation Report). The laboratory also ensured that the LDT was validated with MTM and heat inactivation as per CLIA 42 CFR.493.1253 and per the requirements listed in the FDA's Molecular Diagnostic Template for Laboratories for LDT EUAs (See Attachment D5400_8_CA_VALRPT_LAB_003). The LDT developed by the laboratory was following federal guidance from the FDA (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-coronavirus-disease-2019-tests-during-public-health-emergency-revised). Reportable range and reference intervals are not applicable for this assay since it is a qualitative assay (Please see Attachment D5400_5_LDT Validation Summary.pdf)

**(2) Patient Impact:** The LDT validation was complete before the first patient samples were accepted on November 1, 2020. During the validation phase of the laboratory set-up, between Oct 19-24, 2020; the following activities were performed to validate an LDT assay, which included validation of all steps to allow for safe

transportation of the samples from all collection sites and safety of the laboratory personnel (Please see Attachment D5400_5_LDT Validation Summary.pdf)

**(3) Preventative Measure: Further test validation of new tests**: In the future, will continue to follow CLIA regulations and FDA guidance, as well as laboratory best practices, for the benefit of our patients in California. In terms of the present assay, we have submitted evidence to demonstrate that no further validation is required. We continue to closely abide by the FDA and CMS guidance of current laboratory practice, please see the attached LDT- SOP for samples processing from accessioning to RNA extraction to PCR in the laboratory.

**(4) Monitoring Mechanism:** The laboratory SOPs are evaluated for uniformity of the data through QA/QC process and updated as needed.

***--------- Response End ---------***

The allegation of compliance is not credible, and the evidence of correction is not acceptable.

a. Review of the EUA and IFU for Perkin Elmer New Coronavirus Nucleic Acid Detection Kit (01/12/2021) indicated, "Perkin Elmer MUST further evaluate the clinical performance from ASYMPTOMATIC individuals in an FDA agreed upon post authorization clinical evaluation study within 30 calendar days of the date of this letter. Labeling updates must be made after submission to FDA."

In its submission, the laboratory stated in the immediate corrective action:

> "The laboratory reviewed the current IFU (version 6) to confirm that use in asymptomatic individual is appropriate."

To correct this deficiency, the laboratory must:

- Provide the supporting documentation regarding the statement in the EUA/IFU that "Perkin Elmer MUST further evaluate the clinical performance from ASYMPTOMATIC individuals in an FDA agreed upon post authorization clinical evaluation study within 30 calendar days of the date of this letter. Labeling updates must be made after submission to FDA."

***--------- Response Start ---------***

**(1) Immediate Corrective Action:** As agreed upon with the FDA, PerkinElmer (Waltham, MA), will be conducting the post authorization clinical study for the asymptomatic claim in the EUA/IFU version 7 (Please see Attachment D5400_3_PerkinElmer New Coronavirus Nucleic Acid Detection Kit -v7.0). Please reference attachment (Attachment D5400_2_LFS Letter May 2021).

**(2) Patient Impact:** The IFU authorizes the laboratory to perform testing of asymptomatic patients. Through the transition to the LDT there is no evidence that the intended use has changed. Therefore, there is no patient impact.

**(3) Preventative Measure:** The CDPH Branch Laboratory continues to monitor changes to the IFU, specifically surrounding asymptomatic testing. When changes to the IFU are released the laboratory will evaluate the impact to its LDT and take action where necessary.

**(4) Monitoring Mechanism:** The quality assurance team within the CDPH Branch Laboratory continues to monitor changes to the IFU as part of the quality management review monthly, specifically surrounding asymptomatic testing. When changes to the IFU are released the laboratory will evaluate the impact to its LDT and take action where necessary.

***--------- Response End ---------***

b. Interpretation of Test Results

In its submission, the laboratory stated the following data analysis timeline for the interpretation of test results:

1. 10/28/2020 to 11/11/2020- results were reported as per the IFU
2. 11/11/2020 to 12/11/2020- a lower Ct cutoff was set for positive results based on Ct value observed during validation, reflecting a change in interpretation from the IFU
3. 12/11/2020 to 01/25/2021- high Ct values (>37-<42 was interpreted as inconclusive
4. 01/25/2021-present- high Ct values (>37-<42 was interpreted as presumptive positive

To correct this deficiency, the laboratory must:

- The laboratory's current interpretation of results is not indicated in the IFU of the EUA. Provide documentation, i.e. current as well as historical data generated at the CDPH Branch Laboratory (Valencia Branch Laboratory) to validate the laboratory's current interpretation of results as of 01/25/2021. You may also provide any additional data demonstrating you established performance specifications prior to adopting the current result interpretation to show compliance with this regulation.

***--------- Response Start ---------***

**(1) Immediate Corrective Action:** The best clinical interpretation for low viral load (high Ct values) was determined by the original lab directors Dr. Shantelle Lucas and Dr. Haleh Farzanmehr and subsequently has been also reviewed by Dr. Rosendorff when he joined on January 27, 2021, the California Department of Public Health leadership (CDPH), the CA governor's Testing Task Force (TTF) and other program stakeholders including a team of lab directors from other CDPH laboratories.

"At the time of the validation study and review of the report there was not comparable assay on the market to make a comparison of the higher sensitivity of the assay. Because of this the laboratory directors were uncomfortable with calling samples in this range as detected. The changes made in December only changed the way the result was worded to the patient. For formal reporting to the state and local health jurisdictions, these results continued to be termed as "inconclusive". As transmission rose, and as the state received feedback from patients and partners, we recognized that the term inconclusive was not instructive and did not provide sufficient direction to patients. In order to alleviate confusion, and in the interest of public health given the spike in cases at the time, we provided clearer direction to the patient to isolate and be retested." (Please see Attachment D5400_1_Dr. Kimsey Letter)

The clinical significance of high Ct values is a subject of scientific debate. Although the IFU gives only a positive or negative interpretation, a clinical decision was made to interpret high Ct values differently from negative or no Ct values. Note that is a post-analytical interpretative decision. This is not a change to the method described in the IFU and has no impact on the performance of the assay. Since the clinical significance of high Ct values is

not yet established, therefore, the current interpretations are appropriate. We have confirmed the analytical sensitivity and specificity by demonstrating the presence of virus in the high Ct values samples by sequencing (Please see Attachment D5400_4_Covid High Ct NGS Data Report 3-2021 v7.pdf). The attached white paper has also been submitted to FDA and for publication in a peer reviewed journal.

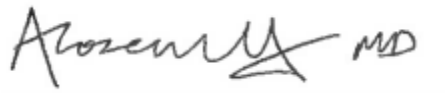
**(2) Patient Impact:** A presumptive positive result indicates that the sample had a low presence of the virus The recommended follow-up was for the patient to self-quarantine and be retested. This is a conservative clinical approach that is unlikely to result in patient harm. Ct values are not part of the patient report, however they are provided by the laboratory director, to authorized CDPH staff, upon request and are used at the provider's discretion when making individualized treatment decisions.

**(3) Preventative Measure:** Any change in clinical interpretation will be reviewed with Laboratory Director Dr. Rosendorff, the California Department of Public Health leadership and other program stakeholders to ensure that patients are given information in accordance with, and healthcare recommendations based on current scientific and clinical understanding. Since changes to the Ct cutoff values is a clinical reporting decision, no validation is required.

**(4) Monitoring Mechanism:** Scientific understanding of and clinical recommendations for cases with load viral load (high Ct values) will continue to change as new information is reported. The best clinical recommendations will be evaluated in accordance with CDPH recommendations, and state and federal guidelines.

***--------- Response End ---------***

Sincerely,



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