A laboratory developed test (LDT) is a type of in vitro diagnostic test that is designed, manufactured, and used within a single laboratory. Therefore, the ORAL RAPID ™ must undergo clinical validation studies in individual high-complexity CLIA certified laboratories. It cannot be designed or manufactured completely, or partly, outside of the laboratory that offers and uses them. The test requires administration performed by a healthcare professional, trained by the respective high complexity laboratory. Although results can be read onsite, they are not official until uploaded to the test platform and validated by the Lab Director. For more information, please visit:

https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests

https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html

Each laboratory which develops this device must conduct their own validations as those which were conducted by *Applied Ingenuity Laboratory.*

Re: Regulatory Landscape and Clinical Performance of ORAL RAPID ™

The regulatory landscape for COVID19 testing is complicated and undergoing revision constantly. However, there are two pathways for regulatory approval and clearance of the **ORAL RAPID ™** Antigen Test.

A. EUA

B. LDT

The main body governing diagnostic testing is the FDA under which laboratories are regulated by CLIA (the Centers for Medicare & Medicaid Services under the Clinical Laboratory Improvement Amendments). During the current pandemic, the FDA authorized for Emergency Use (EUA) the initial RT-PCR test for COVID19 which remains the gold-standard for COVID19 diagnostics. They also implemented a process for laboratories and manufacturers to submit clinical performance documentation for EUA approval of other products or variations of existing laboratory protocols for COVID19 diagnosis.

Historically, the FDA **has not objected** to commercial manufacturers developing and distributing COVID-19 test kits to healthcare workers for point-of-care testing **after validation** of the test **and before EUA submission.** However, as of last week, the FDA banned commercial manufacturers from the sale of their Antigen Rapid Tests until they **obtain full FDA EUA approval**

In an effort to reduce regulatory burden, on August 19, 2020, the U.S. Department of Health and Human Services (HHS) announced the rescission of guidance's and other Food and Drug Administration (FDA) issuances concerning review of Laboratory Developed Tests (LDTs). HHS said FDA will not require premarket review of LDTs "absent notice-and-comment rulemaking, as opposed to through guidance documents, compliance manuals, website statements, or other informal issuances." HHS added that

those clinical laboratories seeking approval, clearance, or an emergency use authorization (EUA) for an LDT may still submit a premarket approval application/premarket notification/EUA request, but they are not required to do so.

The **ORAL RAPID ™** test has undergone clinical validation in the high-complexity CLIA certified laboratory Applied Ingenuity Diagnostics and can be performed as an LDT by Applied Ingenuity Diagnostics. Our clinical validation data is provided below.

Intended Use

The **ORAL RAPID ™** test is a lateral flow antigen test for the qualitative detection of the SARS-CoV2 nucleocapsid from either upper or lower respiratory specimens (such as nasal, nasopharyngeal or oropharyngeal swabs, sputum, or aspirates collected from individuals suspected of COVID19 by a healthcare provider.

Testing is limited to Applied Ingenuity Diagnostics or other laboratories designated by Applied Ingenuity Diagnostics that are also certified under the CLIA regulations.

Results are for the identification of SARS-CoV-2 antigen. The SARS-CoV-2 antigen is generally detectable in respiratory specimens during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 virus; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status. Positive results do not rule out bacterial infection or co-infection with other viruses. The agent detected may not be the definite cause of disease.
Laboratories within the United States and its territories are required to report all positive results to the appropriate public health authorities.
Negative results do not preclude SARS-CoV-2 infection and should not be used as the sole basis for patient management decisions. Negative results must be combined with clinical observations, patient history, and epidemiological information.

Testing with the COVID19 **ORAL RAPID ™** test is intended for use by trained clinical laboratory or medical personnel specifically instructed and trained in the techniques of sample collection under medical or CLIA license. The **ORAL RAPID ™** test is only for use under the CLIA LDT pathway by Applied Ingenuity Diagnostics.

Device Description

The **ORAL RAPID ™** antigen test kit is a lateral flow qualitative immunoassay for the rapid determination of the presence or absence of SARS-CoV-2 in human oropharyngeal specimens. The test kit comes with an oropharyngeal swab with 30 mm break-point, test cartridge, sample dilution buffer, mixing tube, and a package insert. The testing cartridge has two detection bands, including a distal control band that appears when the sample has flowed to the end of the testing strip. The presence of SARS-CoV-2 antigen are indicated by a red/purple line in the specific region indicated on the device

Performance Evaluation

1. Analytical Sensitivity

Limit of Detection Study

The LOD study established the lowest concentration of SARS-CoV2 virus that could be detected by the **ORAL RAPID ™** test. The preliminary LOD was established by testing clinical samples for which genome copies (cp/ul) were established by RT-PCR. Replicates were tested for reproducibility.

The preliminary LOD was confirmed to be approximately 10,000 copies/ul.

2. Analytical Specificity

Cross-reactivity of the COVID19 **ORAL RAPID ™** test was evaluated using testing clinical samples of whole organisms on the **ORAL RAPID ™** test platform.

Organism	RT-PCR	COVID RTPCR	ORAL RAPID ™
Influenza B	Positive	Negative	Negative
Strep Pneumonia	Positive	Negative	Negative
E. Coli	Positive	Negative	Negative
K. Pneumoniae	Positive	Negative	Negative
Citrobacter	Positive	Negative	Negative
Human Rhinovirus	Positive	Negative	Negative
Coronavirus 229E	Positive	Negative	Negative
Mycoplasma Pneumoniae	Positive	Negative	Negative

3. Clinical Evaluation

A contrived clinical study was performed to evaluate the performance of the **ORAL RAPID ™** test. A total of 80 clinical respiratory samples were tested. Negative samples were negative by RT-PCR. Positive samples were chosen at 1X LOD or higher. Samples were in VTM. A nylon swab was placed into each sample and swirled for 15 seconds and then treated according to the **ORAL RAPID ™** protocol.

	CDCEUA Positive (n=30)	CDCEUA Negative (n=50)
ORAL RAPID™ Positive	**28**	**1**
ORAL RAPID™ Negative	**2**	**49**
Total	**30**	**50**

Statistic	Value	95% Confidence Interval
Sensitivity	**93.3**	**77 – 99%**
Specificity	**98.0**	**89-99%**

The **ORAL RAPID ™** test has similar if not better performance (based on published reports) to the Sofia antigen test. Applied Ingenuity Diagnostics will begin to offer the test as a Laboratory Developed Test under the CLIA guidance for LDT performance. The test will need to be administered by a healthcare professional trained by Applied Ingenuity Diagnostics. Although results can be read onsite, they are not official until uploaded to our Test platform and validated by the Lab Director.

If you have any questions or concerns, feel free to contact us.

Sincerely,

Maulik Shah
_____, **MD PhD**

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