Taking on the Pandemic: How L7's ESP Enables Rapid Response to COVID-19

L7INFORMATICS

Figure 1: ESP Platform Diagram

INTRODUCTION

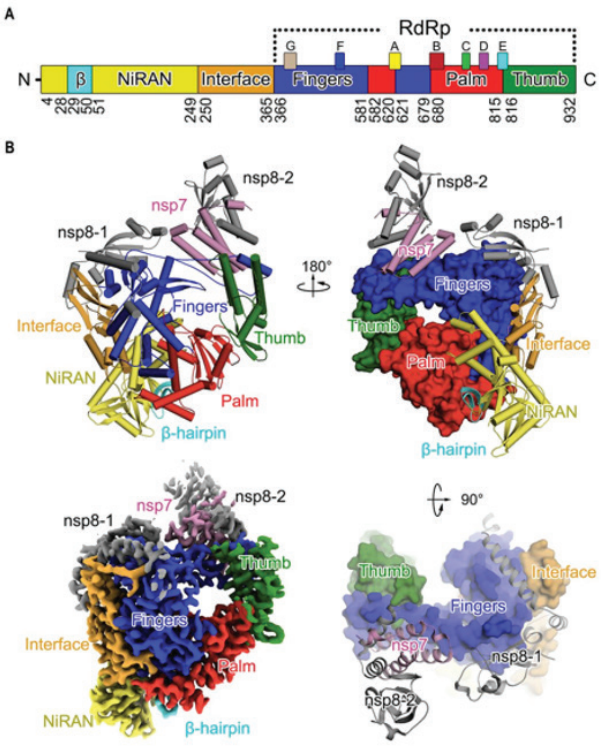
L7's mission is to revolutionize the scientific process by streamlining process and data management and thereby accelerate precision health across research, diagnostics, medicine, therapeutics, and agriculture. The Enterprise Science Platform, or ESP, is a unified platform that provides a common data model, tooling, and architecture that spans a user's business process; thereby eliminating the need to purchase and integrate point solution software applications. ESP enables users to increase capacity, develop predictive data models, improve data collaboration and reporting within a single regulatory-compliant platform that spans their entire business operation.

COVID-19 RESPONSE

The current pandemic is an accelerated case study in the importance of integrating workflows and data management. With COVID-19, we have seen great advancements in scientific knowledge at the molecular level to enable virus-specific testing and the development of new therapies.

Structure of COVID-19 virus nsp12-nsp7-nsp8 complex. (A) Domain organization of COVID-19 virus nsp12. The interdomain borders are labeled with residue numbers. The N-terminal portion with no cryo-EM map density and the C-terminal residues that cannot be observed in the map are not included in the assignment. The polymerase motifs are colored as: motif A, yellow; motif B, red; motif C, green; motif D, violet; motif E, cyan; motif F, blue; and motif G, light brown. (B) Ribbon diagram of COVID-19 virus nsp12 polypeptide chain in three perpendicular views. Domains are colored the same as in (A). The individual nsp8 (nsp8-1) bound to nsp12 and that in the nsp7-nsp8 pair (nsp8-2) are in grey; the nsp7 is in pink. The bottom left panel shows an overview of the cryo-EM reconstruction of the nsp12-nsp7-nsp8 complex.

Structure of COVID-19 virus complex (Yan Gao et al. Science 2020)



Science AAAS

Figure 2: Structure of COVID-19 virus complex (Yan Gao et al. Science 2020)

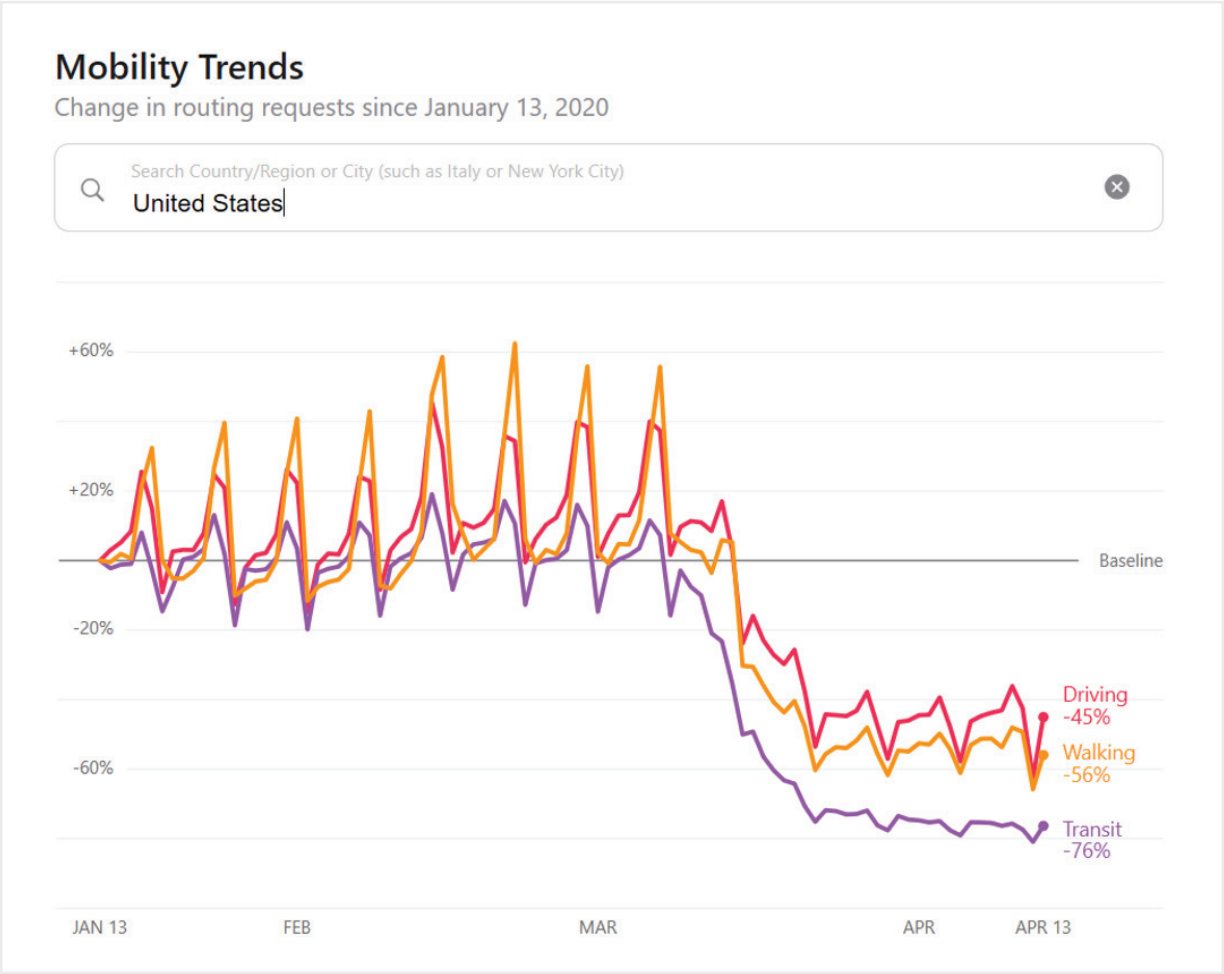


Figure 3: Mobility Changes During COVID-19 Pandemic (www.apple.com/covid19/mobility)

We've also seen how real-time epidemiology and mass communications can yield benefits at the population level through stay at home practices to "flatten the curve".

While these advancements have enabled better population level prevention and targeted treatments, deficiencies in workflow and data management have limited a more proactive and targeted response.

GAPS IN COVID-19 WORKFLOW AND DATA MANAGEMENT

The initial testing response, which required CDC confirmation, was limited for many reasons including reagent availability, testing capacity, and evolving testing requirements. Once the FDA opened testing to commercial labs on Feb 29, this constraint was lifted and testing capacity increased; however, testing capacity remains capped below 180,000 tests per day through mid-April, in part to limitations in testing reagents.

Although we are beginning to address the limitations in testing platforms and available reagent supplies for COVID-19 detection by PCR, testing remains restricted to high risk patients (www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html).

As monitoring moves from the largely binary outcomes of PCR testing for confirming COVID-19 exposure to semi-quantitative measures of immuno-protection with serology testing, scientific interpretation becomes even more difficult.

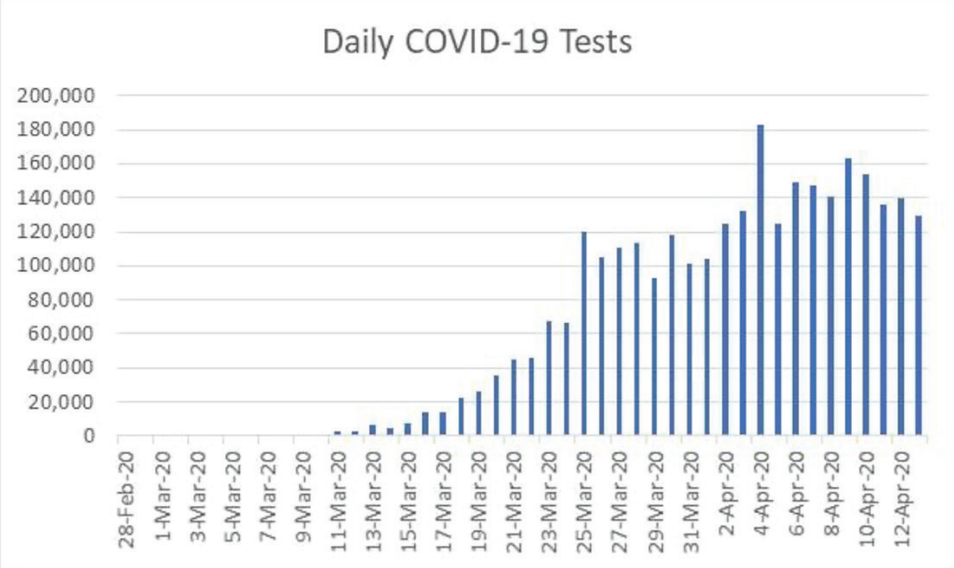


Figure 4: Total COVID-19 Daily Testing – US (https://covidtracking.com)

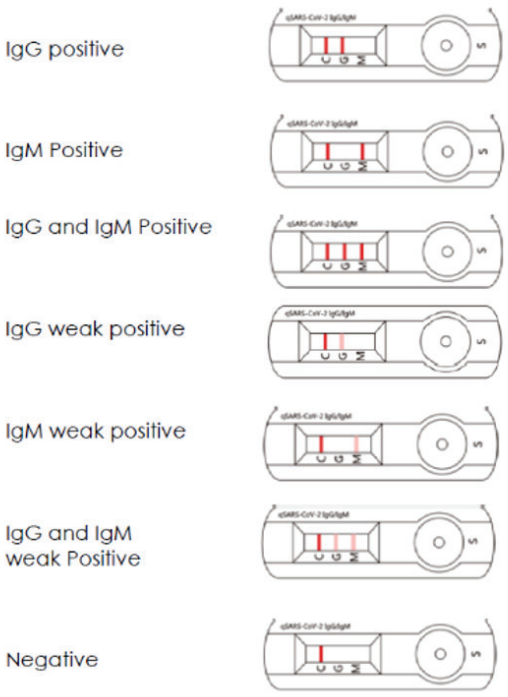


Figure 5: Cellex™ qSARS-CoV-2 IgG/IgM Rapid Test Instructions (www.cellex.com)

Negative results do not rule out SARS-CoV-2 infection, particularly for patients who have been in contact with known infected persons or in areas with high prevalence of active infection. Follow-up testing with a molecular diagnostic test is necessary to rule out infection in these individuals. Results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection.

False positive results may occur due to cross-reacting antibodies from previous infections, such as other coronaviruses, or from other causes.

Samples with positive results should be confirmed with alternative testing method(s) and clinical findings before a diagnostic determination is made.

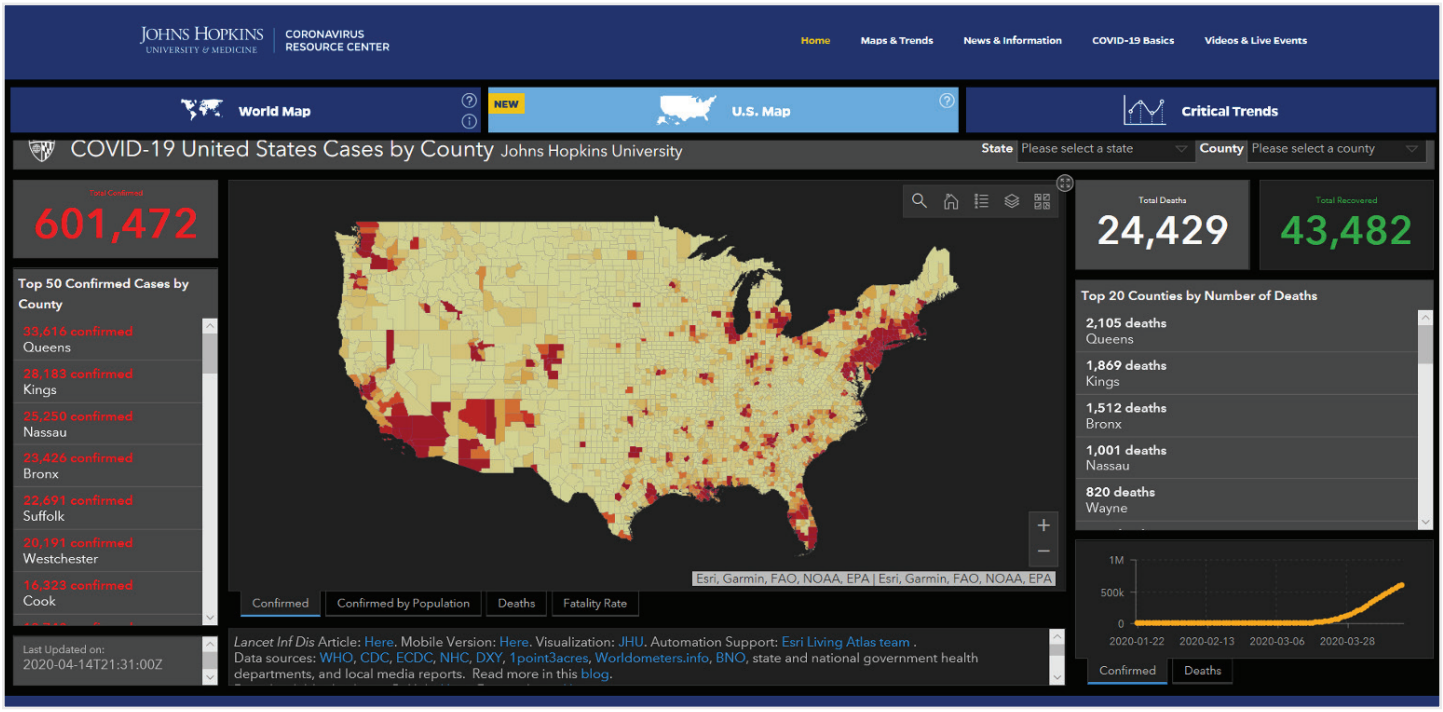


Figure 6: Johns Hopkins COVID-19 Tracking Dashboard (https://coronavirus.jhu.edu)

Additionally serology testing methodologies are more varied than molecular detection assays (www.finddx.org/covid-19/) and local laboratory specifics can make comparing antibody results across laboratories difficult.

Finally, testing data is buried in siloed local systems such as LIMS and EMR within each lab and health system respectively thereby turning the compilation and reporting of testing data into a major effort which is currently being managed by academic and private organizations.

While aggregate data works for population level responses, it limits more scientific discrimination and targeted responses because it is difficult to separate the disease from the patient in the absence of randomized clinical trials – complicating both the treatment of individuals as well as the testing of new therapies (www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments).

NEXT GENERATION DIGITAL PLATFORMS FOR COVID-19 TESTING

We believe that the use of digital platforms to provide better integration of the science, laboratories, and data management like those being developed by Contamination Source Identification (CSI) should provide higher fidelity data and enable more comprehensive interventions. These digital platforms need an exchange for standardizing, adapting, and distributing testing methods because they provide a critical context for data interpretation.

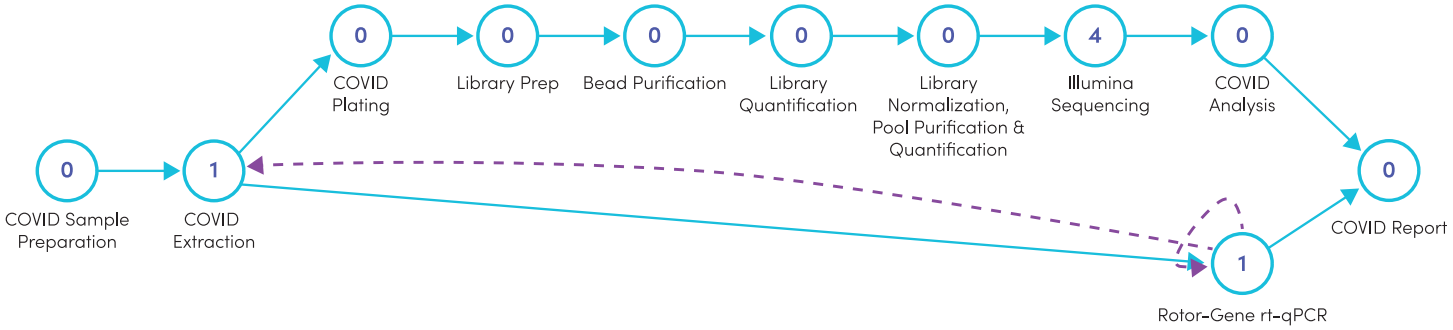


Figure 7: ESP COVID-19 Workflow Chain

The platforms also need to have an interchangeable data model that facilitates combining different testing result data formats (e.g. PCR, NGS, Ab) to identify correlations, evaluate immunological responses, and provide longitudinal data.

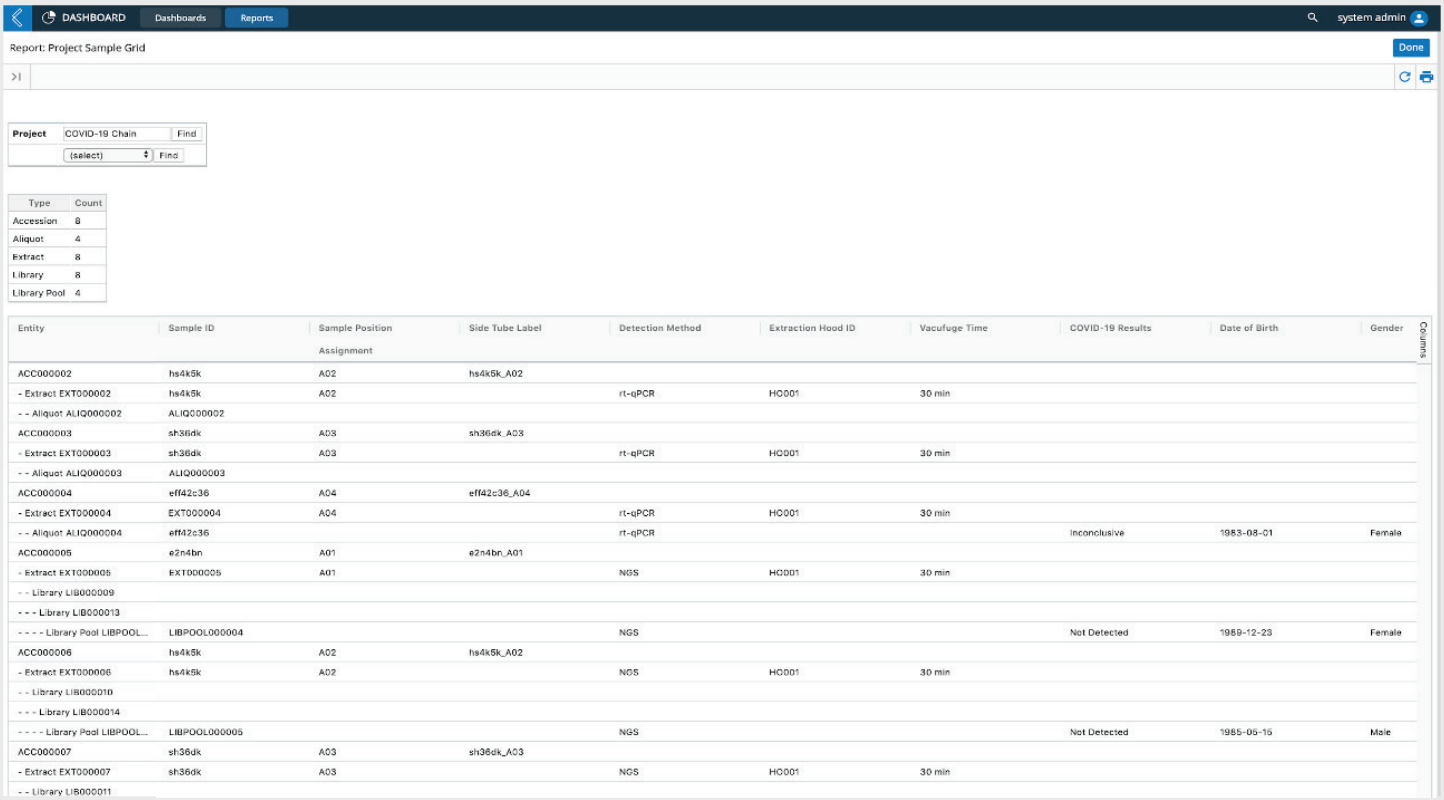


Figure 8: ESP Flexible Data Models

Finally, the ability to perform modeling of virus shifts and drifts while integrating patient data vs outcomes would give us the opportunity to move to a more proactive data-driven response to both improve individual treatment decisions as well as provide contemporary real world evidence against which novel treatments can be judged. The critical nature of testing for both the medical and economic recovery moving forward is becoming increasingly clear.

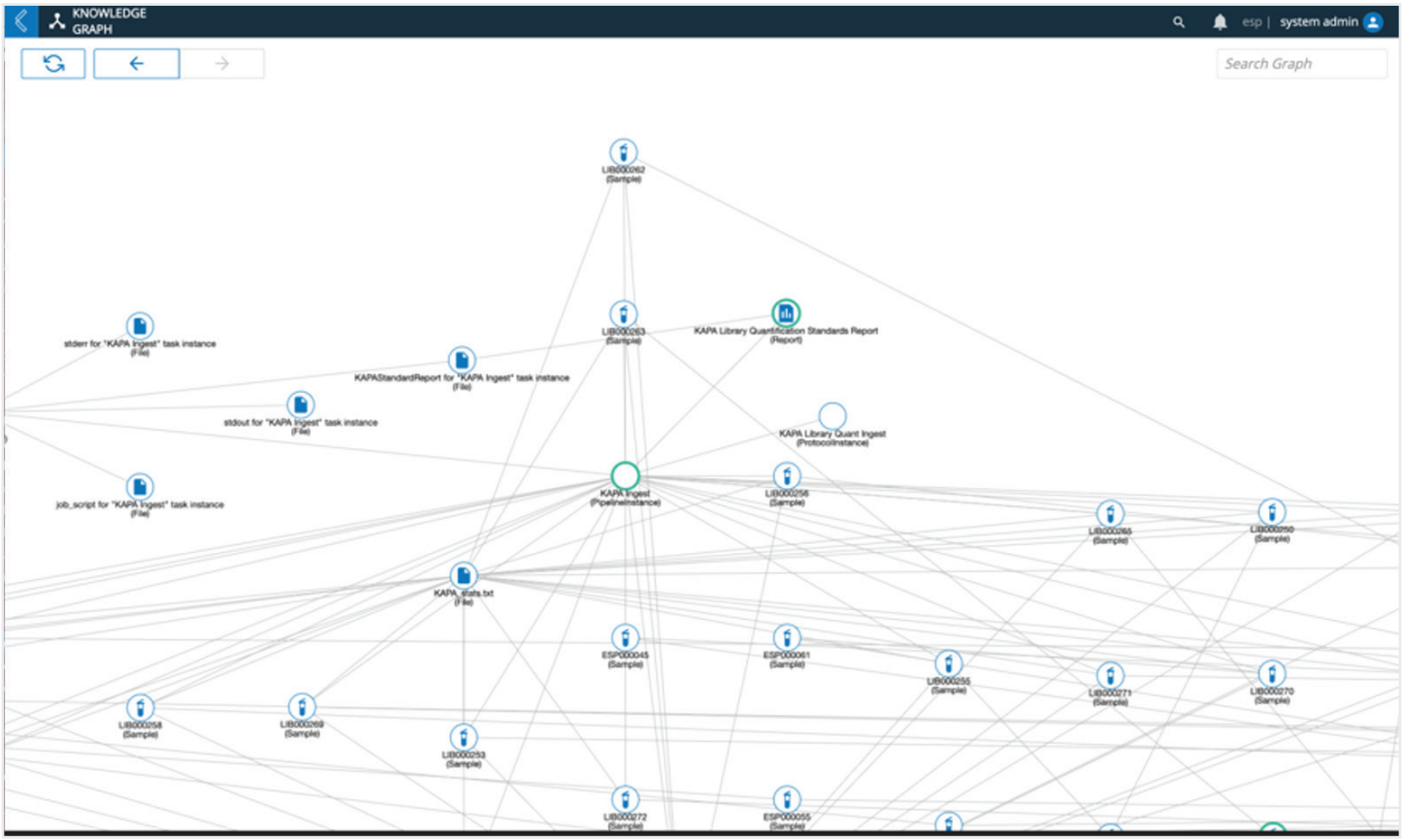


Figure 9: ESP Knowledge Graph

CSI CASE STUDY

Contaminant Source Identification (CSI) is a CLIA approved testing laboratory focused on the detection of bacteria in patient samples and is currently engaged in ongoing clinical sample validation trials of the CSI-Dx™ platform for Lyme disease to be followed by trials in sepsis, meningitis, pneumonia and C. *difficile*. In 2019, CSI implemented L7's ESP platform for maintaining efficiency and compliance through an automated LIMS interface that manages:

- Data Tracking
- Protocols and Personnel Tracking
- Instrument Tracking
- Reagent Tracking
- Automated Accessioning and Reporting

In response to the need for COVID-19 testing in rural Pennsylvania communities, CSI partnered with local medical institutions to conduct clinical and analytic validation of CSI's RAPID-Dx test system for COVID-19 (www.cnn.com/2020/04/07/us/amish-coronavirus-drive-through-testing-horse-and-buggies-trnd/index.html). In parallel to assay validation, CSI and L7 developed and qualified an integrated LIMS workflow for the COVID-19 diagnostic testing in less than 2 weeks. This rapid timeline was enabled through ESP's flexible data modeling and leveraging ESP's portable content from the existing CSI lyme disease workflows.

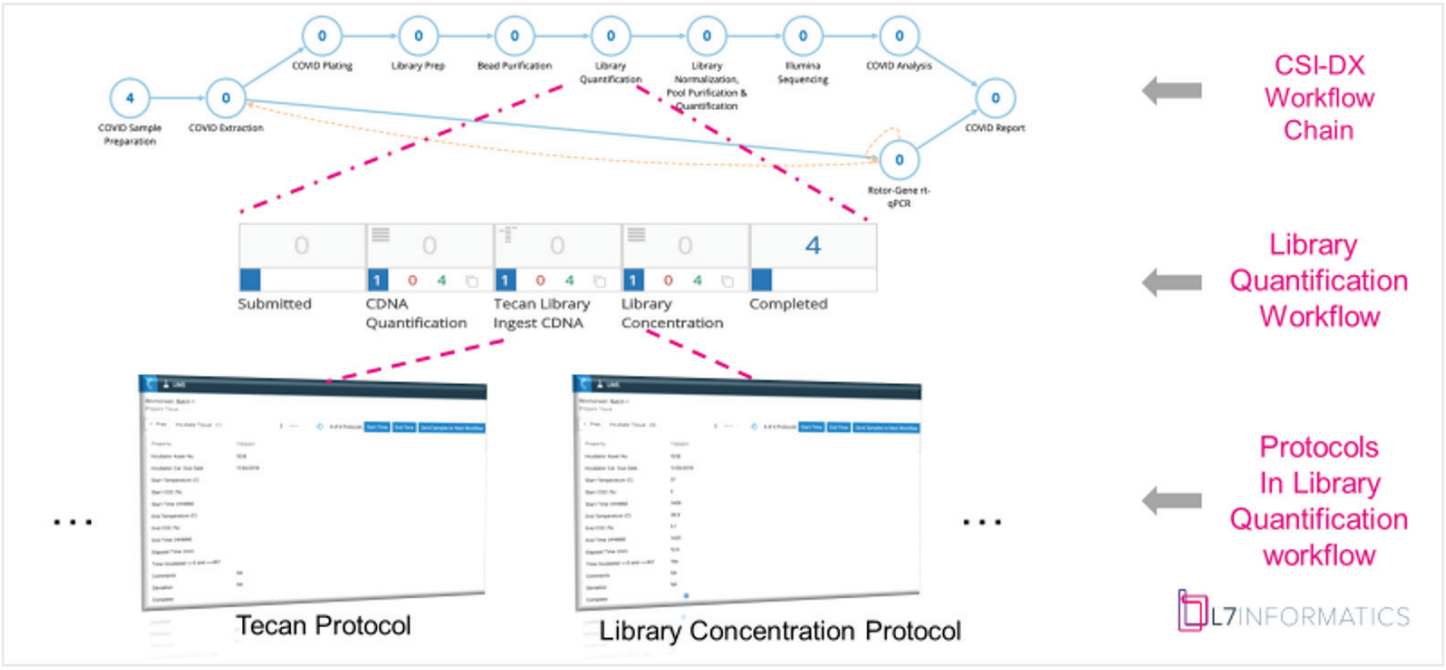


Figure 10: Repurposing CSI Lyme Disease Workflow to COVID-19

CSI's diagnostic approach to COVID-19 includes standard extraction and purification steps followed by either next gen sequencing or qPCR analysis. The results are then analyzed and assembled into a clinical report that is provided to the physician.

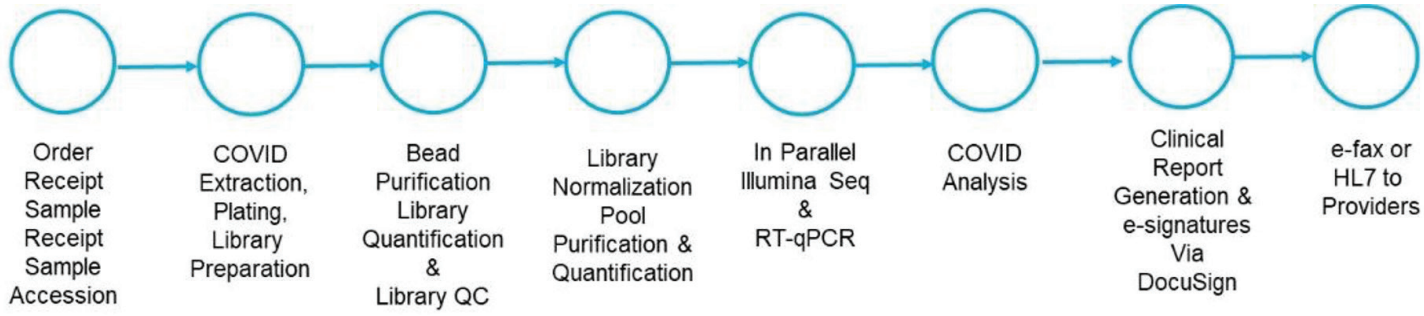


Figure 11: CSI COVID-19 Workflow Chain

Initial testing orders are recorded in ESP through a sample accessioning applet that enables CSI to record patient and hospital information along with sample identification to kick off the laboratory operations in 20% of the time and resources required using hand-recorded entries.

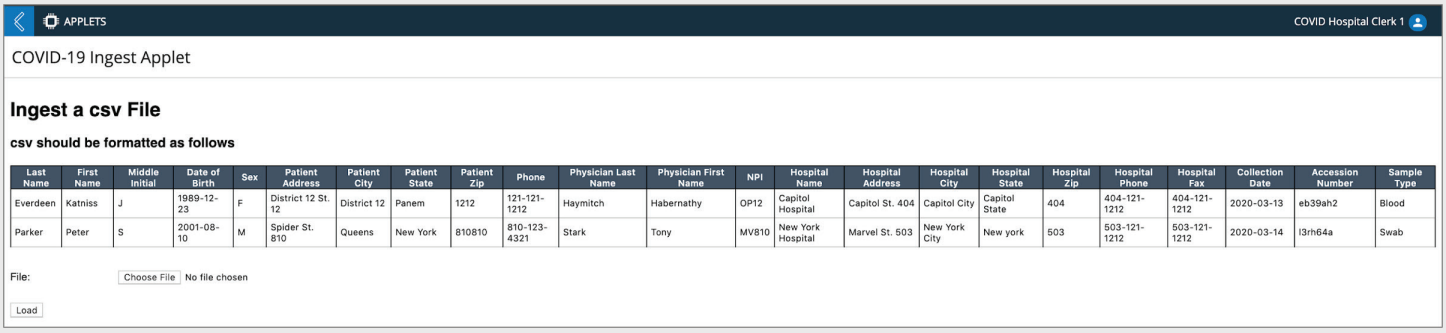


Figure 12: Sample accessioning

Assay execution is then managed real time within ESP workflows that detail the execution and data collection status of each sample.

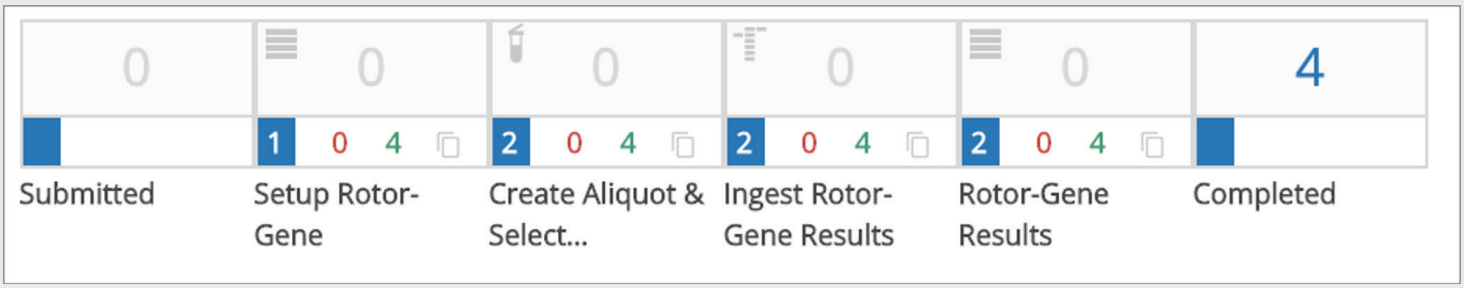


Figure 13: rt- qPCR Sample Workflow

Analyses are performed both within ESP as well as calling out to external bioinformatics pipelines as needed (i.e. NGS).

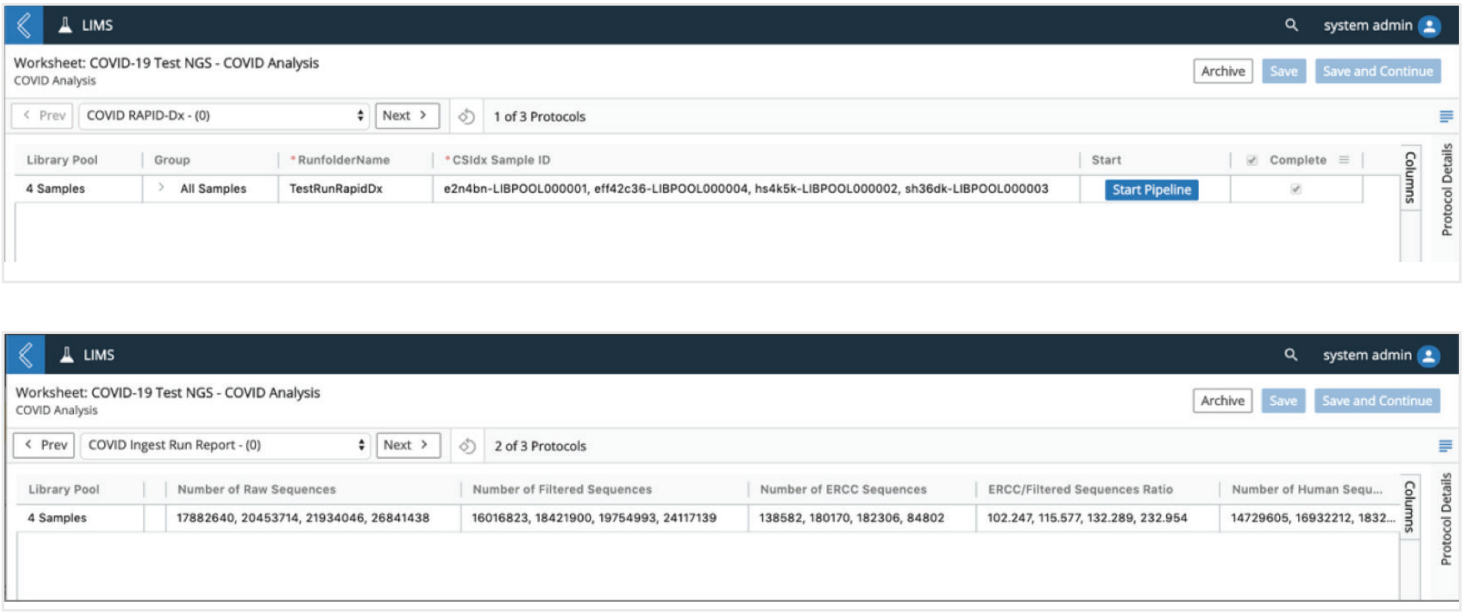


Figure 14 :NGS Pipeline Initiation and Results Ingest

Rotor-Gene Standard Report, 2020-04-03T16:23:40.573906

Expected Controls Results

Control Type	Name	2019 COV N1	2019 COV N2	RP	Expected CT Values
Extraction	HSC	-	-	+	<40 CT
Negative	NTC	-	-	-	None
Positive	nCoVPC	+	+	+	<40 CT

Controls Results

Control	Replicate 1	Replicate 2	Replicate 3
HSC	19	35	23
NTC	51	21	33
nCoVPC	236	532	162

Samples Results

Type	Name	N1	N2	RP
	az9qz	39	21	14
	dc7ec	3	39	27
	ed1zx	12	12	35
	fv6rv	29	27	39
	gb5tb	7	19	40
	hn4yn	2	87	45
	ik6gh	45	12	35
	jm3um	43	56	23
	ol0nm	9	50	50
	ol7bn	5	74	23
	pl8ui	34	56	96
	pm9jk	12	43	67
	qa2qw	23	43	74
	rf2er	22	32	13
	sx8wx	35	40	16
	tg3df	78	5	33
	ub0op	7	40	40
	uj5ty	65	46	57
	vy9kl	5	20	20
	ws1as	34	32	57
	yh4cv	12	23	97

Figure 15: COVID-19 rt-qPCR Test Analysis

Results for samples and controls are compiled and assessed against defined assay acceptance criteria to generate test analysis reports.

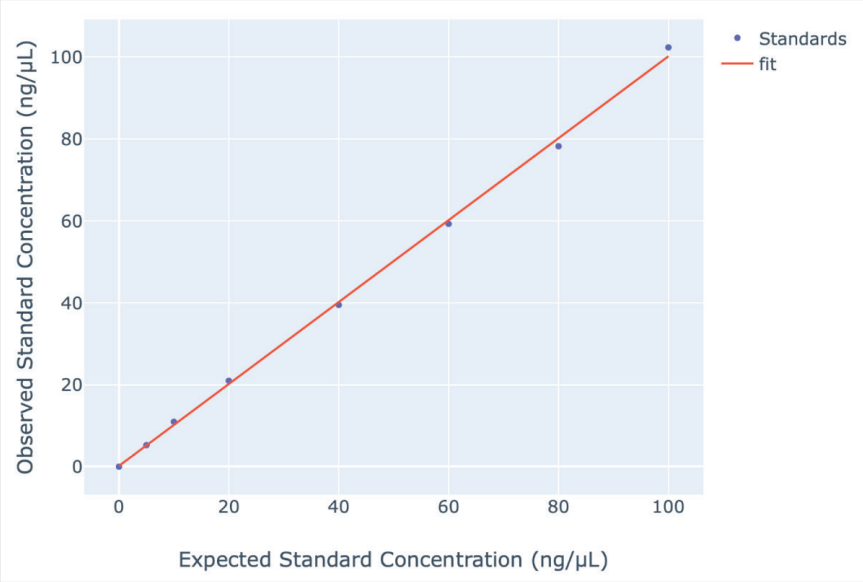


Figure 16: Automated Standard Curve Report

The sample test results can also be accompanied by assay performance analytics such as standard curve fit to ensure consistency in assay performance.

Worksheet: COVID-19 Test NGS - COVID Report
COVID Report

Archive Save

Prev | COVID Report - (3) | Next | 1 of 1 Protocols

Columns | Protocol Details

Property	LIBPOOL000001	LIBPOOL000002	LIBPOOL000003	LIBPOOL000004
Detection Method	NGS	NGS	NGS	NGS
COVID-19 Results	Not Detected	Not Detected	+ 2019-nCOV	+ 2019-nCOV
Report Result	Not Detected (Negative)	Not Detected (Negative)	Detected (Positive) [CRITICAL]	Detected (Positive) [CRITICAL]
Sample ID	e2n4bn	hs4k5k	sh36dk	eff42c36
Collection Date	3/26/2020	3/26/2020	3/26/2020	3/26/2020
Sample Type	Swab	Swab	Swab	Swab
Patient Last Name	Pope	Leduc	Matthews	Targaryen
Patient First Name	Olivia	Antoine	Taylor	Daenerys
Date of Birth	12/23/1989	5/15/1985	12/23/1986	8/1/1983
Gender	Female	Male	Unknown	Female
Physician Last Name	Rosen	Rosen	Rosen	Rosen
Physician First Name	David	David	David	David
Physician Phone	5031211212	5031211212	5031211212	5031211212
Physician Fax	5031211212	5031211212	5031211212	5031211212
File Link	Final Report			
*File UUID	9d626a70-2353-4132-8868-1e48a94265f6			
Start	✓done	Start Pipeline	Start Pipeline	Start Pipeline
Complete	☑	☐	☐	☐

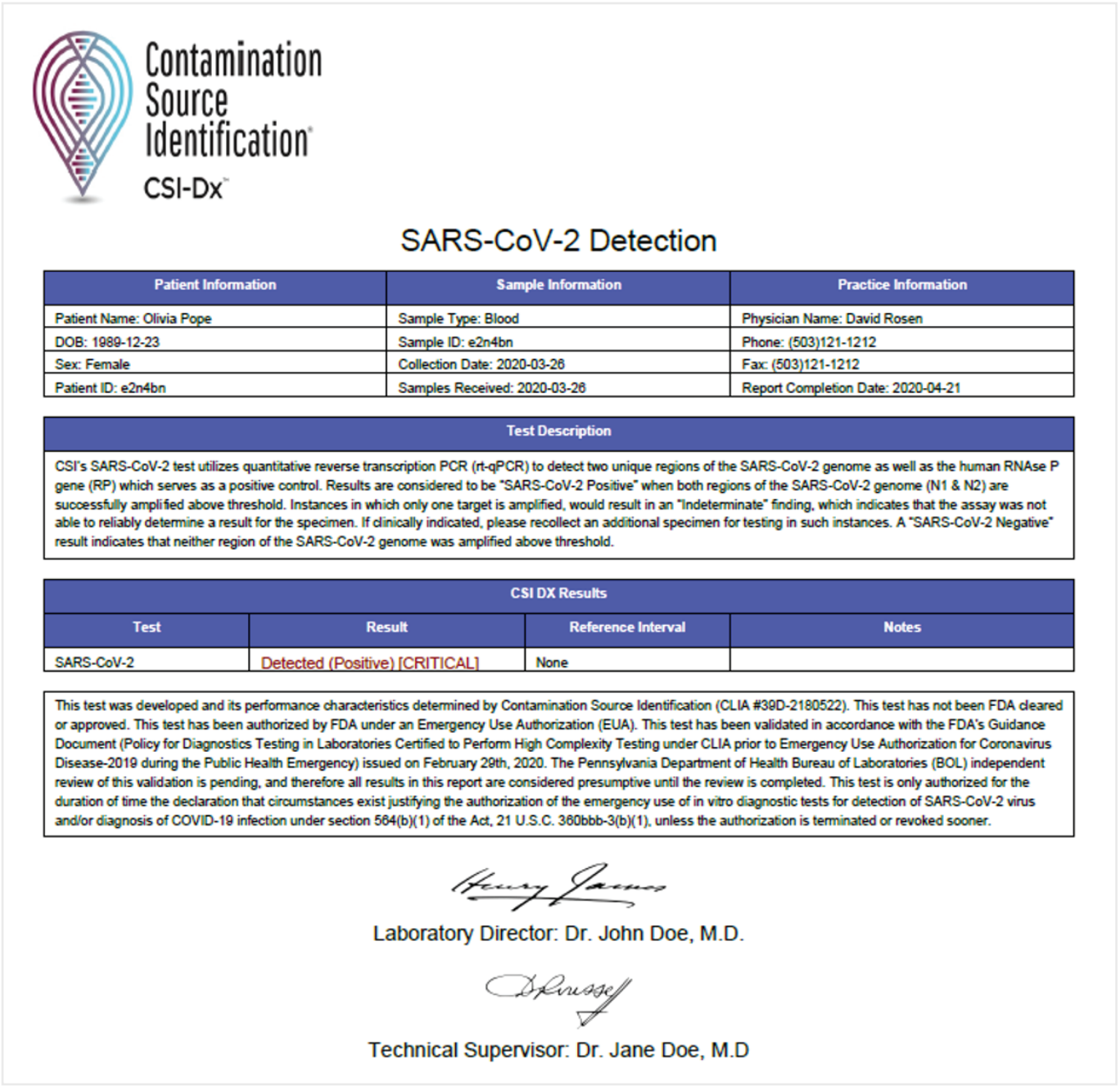
Figure 17: Final Test Results Summary

Finally testing results can be compiled and related back to initial sample accessioning data in order to prepare data for reporting.

Physician-ready are generated within ESP and delivered electronically to the requesting laboratory.

CONCLUSION

The rapid onset of the COVID-19 pandemic has sparked a need for swift action from diagnostic labs across the country. Like CSI, many laboratories have been seeking to respond to this need and rapidly develop assays focused on the molecular detection of COVID-19 for treatment decisions and will soon begin to include immuno-assays in order to meet the testing criteria for the US economic recovery plan (www.whitehouse.gov/openingamerica/#criteria). In order to enable rapid re-tooling and increased laboratory capacity demands, software solutions like L7's ESP can provide a comprehensive LIMS platform that permits efficient, accurate and timely processing of these critical tests.



Contamination Source Identification
CSI-Dx

SARS-CoV-2 Detection

Patient Information	Sample Information	Practice Information
Patient Name: Olivia Pope	Sample Type: Blood	Physician Name: David Rosen
DOB: 1989-12-23	Sample ID: e2n4bn	Phone: (503)121-1212
Sex: Female	Collection Date: 2020-03-26	Fax: (503)121-1212
Patient ID: e2n4bn	Samples Received: 2020-03-26	Report Completion Date: 2020-04-21

Test Description
CSI's SARS-CoV-2 test utilizes quantitative reverse transcription PCR (rt-qPCR) to detect two unique regions of the SARS-CoV-2 genome as well as the human RNAse P gene (RP) which serves as a positive control. Results are considered to be "SARS-CoV-2 Positive" when both regions of the SARS-CoV-2 genome (N1 & N2) are successfully amplified above threshold. Instances in which only one target is amplified, would result in an "Indeterminate" finding, which indicates that the assay was not able to reliably determine a result for the specimen. If clinically indicated, please recollect an additional specimen for testing in such instances. A "SARS-CoV-2 Negative" result indicates that neither region of the SARS-CoV-2 genome was amplified above threshold.

CSI DX Results			
Test	Result	Reference Interval	Notes
SARS-CoV-2	Detected (Positive) [CRITICAL]	None	

This test was developed and its performance characteristics determined by Contamination Source Identification (CLIA #39D-2180522). This test has not been FDA cleared or approved. This test has been authorized by FDA under an Emergency Use Authorization (EUA). This test has been validated in accordance with the FDA's Guidance Document (Policy for Diagnostics Testing in Laboratories Certified to Perform High Complexity Testing under CLIA prior to Emergency Use Authorization for Coronavirus Disease-2019 during the Public Health Emergency) issued on February 29th, 2020. The Pennsylvania Department of Health Bureau of Laboratories (BOL) independent review of this validation is pending, and therefore all results in this report are considered presumptive until the review is completed. This test is only authorized for the duration of time the declaration that circumstances exist justifying the authorization of the emergency use of in vitro diagnostic tests for detection of SARS-CoV-2 virus and/or diagnosis of COVID-19 infection under section 564(b)(1) of the Act, 21 U.S.C. 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Laboratory Director: Dr. John Doe, M.D.

Technical Supervisor: Dr. Jane Doe, M.D

Figure 18: Final report generation

For additional information on how ESP can help streamline your operations, please visit us online or email the L7 team today!

1219 West 6th Street | Austin, TX 78703
888.461.5227 | L7informatics.com | info@L7informatics.com