DOE National Laboratory Capabilities for COVID-19 Response

Executive Summary

This document summarizes the capabilities of DOE's seventeen laboratories that have been used to respond to the threats posed by COVID-19 and are relevant to both near-term responses and longer-term R&D opportunities. The compilation was originally based on input in response to a data call issued in September 2020 to the DOE laboratory representatives on the NVBL 17 Laboratory Working Group and has been updated regularly. These capabilities cover broad experimental, computing, characterization, epidemiological modeling, and manufacturing areas, as outlined below:

Molecular structural determination: X-ray sources and neutron sources at DOE user facilities provide atomic-level resolution macromolecular crystal structures both for studies related to drug and vaccine development and needed for computational modeling. For example, companies that produced all three vaccines administered in the United States accessed DOE x-ray sources during their development. In addition, *cryo-electron microscopes* can be used to provide high resolution structures of virus particles, proteins, RNA and their interactions with antibodies and other drugs. Structures of subcellular components inside cells can be derived from cryo-electron tomograms of vitrified cells in various pathological conditions.

Computational modeling and simulation: High performance computing resources at DOE user facilities, employing artificial intelligence, molecular dynamics simulations, and modeling tools, combined with input from protein structure data, provide information to support research related to rapid survey of existing drugs and development of anti-viral agents and vaccines. These world-leading computational resources have been accessed by hundreds of researchers in academe, industry, and government during the COVID crisis.

Genomic sequencing: Genomic resources at DOE's Joint Genome Institute and other facilities can sequence large numbers of patient samples to identify COVID-19 variants, to identify candidate regions for immuno-targeting, and construct models of individual susceptibility.

Multi-omics analysis: Multi-omics resources at DOE's Environmental Molecular Science Laboratory and other DOE laboratories can characterize identify functional biomarkers for countermeasure and therapeutics development and to predict who is at greatest risk of severe disease and death.

Epidemiological modeling and data analysis: Capabilities in data analysis using computation-based tools, such as geospatial information systems, artificial intelligence, data analytics, and simulations, can yield information for health care providers and government groups on modeling disease spread, screening of travelers for pandemics, collecting/analyzing information and data from open sources world-wide, and providing tools for real-time decision making, risk analysis and prioritization. During the

COVID crisis NVBL has assisted the Centers for Disease Control and Prevention (CDC), as well as state and local decision makers to predict and control disease spread.

Materials and manufacturing to address supply chain bottlenecks: Extensive capabilities and expertise in manufacturing, combined with capabilities at DOE nanoscience research centers and light and neutron sources, have been used to produce new materials and tooling that allowed industry to produce N95 respirators, face masks, sample collection plates, and other critically needed supplies. This effort resulted in the generation of nearly a thousand new jobs.

Innovations in COVID testing: *Expertise in chemical and biological analysis at the DOE laboratories* was leveraged to develop new testing methods and instrumentation for COVID testing, including development of a new non-invasive sampling device based on collection of patient breath. The COVID team also supported the CDC and Food and Drug Administration (FDA) by evaluating imported test kits and prevented faulty kits from reaching the US market. In addition, several laboratories to receive CLIA certification to analyze specimens for diagnostic purposes.

Evaluation of environmental fate and transport: Capabilities in aerosols, building technologies, and computational modeling, were used to assess airborne dispersion and transport of virus, transport of human-expelled droplets and aerosols, and the lifetimes of virus on surfaces. This work provided information about distribution of the virus in built environments (e.g., schools, offices, transportation centers, and restaurants) to support decisions about establishing physical barriers to minimize virus spread.

Design of Molecular Therapeutics: Capabilities for antiviral and antibody design and production draw upon computational, synthetic, structural characterization and production capabilities and expertise across several laboratories. NVBL efforts have yielded a number of high potential antivirals that are currently being evaluated in pharmaceutical laboratories.

Other Resources:
Sophisticated emergency response capabilities include Bio-Safety Laboratories (BSL) at several laboratories capable of handling and studying the COV-19 virus, a mobile emergency response laboratory with biosafety capabilities, and mobile detection platforms to screen samples. Several labs have experience training first responders in biothreat emergencies.

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Ames Laboratory

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In situ studies of dynamic viral response to environments: Liquid phase electron microscopy imaging can perform dynamic studies at 50-200 nm for examining in situ dynamic viral response to physical and chemical factors under realistic conditions. The stimuli/environmental variables that can be considered include temperature, UV radiation, changes in pH and ionic strength, influx of oxidative ions, moisture content, and chemical composition.

Viral fate and antiviral materials: Accelerated materials discovery and design of materials with antiviral/antibacterial characteristics, synthesis expertise from nanoparticulate to bulk fabrication, rapid throughput of surrogate viral testing, incorporation of materials into PPEs and prototyping capabilities

Super-resolution bioimaging: Ames Laboratory bioimaging capabilities provide rapid, three-dimensional chemical imaging and detection at resolutions below the diffraction limit. These approaches have been demonstrated examining cell wall chemistry.

Synthetic biology of key viral proteins: In addition to virus detection, Ames has capabilities to clone viral sequences for synthetic biology, and to synthesize viral proteins with desired sequences, in order to accelerate the development of new therapeutics, and to understand binding between viral proteins and potential therapeutics.

Molecular chemistry codes for exascale computing: Ames Lab researchers are leading the development of open-source codes for quantum chemistry, particularly aimed at current and next-generation high performance computers. These codes enable the treatment of large systems, capable of handling large biological molecules.

In addition to these, our contractor, Iowa State University, has many relevant capabilities. For example, the Nanovaccine Institute, a consortium of 66 researchers at 20 universities, research institutes, national laboratories, and companies, coordinated by Iowa State University. Researchers at the Nanovaccine Institute have recently started a collaboration to develop a COVID-19 vaccine, using a platform technology that is well-suited for vaccine development.

Argonne National Laboratory

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Computational capabilities: Argonne's Leadership Computing Facility supports the COVID-19 High Performance Computing Consortium, and provides supercomputer resources for molecular modeling, bioinformatics, and epidemiology to accelerate the development of treatments and strategies to combat the COVID-19 pandemic. An artificial-intelligence-driven drug development pipeline that is now part of collaborations with U. Chicago, AstraZenca, Jannsen, Chase Cancer Center, and Memorial Sloan Kettering and others. Deep learning, which is 1000x faster than existing methods, is used to design ligands for protein targets from a nearly unlimited space of design options. Using protein structures obtained by macromolecular crystallography for key SARS-CoV-2 proteins, these tools can be used for the development of antivirals and can be adapted for epitope analysis for vaccine development.

Argonne leads the NIAID Bioinformatics Resource Center that supports the infectious diseases research community with computational analysis, machine learning and data integration etc. The Bacterial and Viral Bioinformatics Resource Center (BV-BRC), based at the University of Chicago, combines independent efforts at UChicago and the J. Craig Venter Institute (JCVI) into a common infrastructure. The Center uses machine learning for virus virulence prediction, classification and evolution and supports both bacterial infectious diseases research, the Pathosystems Resource Integration Center (PATRIC) (https://patricbrc.org/), and viruses, the Virus Pathogen Database and Analysis Resource (ViPR) (https://www.viprbrc.org/brc/home.spg?decorator=vipr) with JCVI. ViPR and Influenza Research Database (IRD) resources are hosted at Argonne.

Advanced Photon Source for protein structures: Argonne is home to the Advanced Photon Source (APS), a DOE user facility, that provides access to macromolecular crystallography capabilities for protein crystal structure determination. Small- or Wide-Angle x-ray scattering (SAXS/WAXS) capabilities at the APS can be used to study ligand binding through protein conformational changes. This can be used to down select the number of compounds that go to crystallization trials. Complementing APS capabilities, the *Advanced Protein Characterization Facility has* specialized capabilities for gene cloning, protein expression, purification, crystallization, and structure determination.

Epidemiological modeling and analysis: Argonne can provide modeling of disease propagation through populations, simulate the impact of transportation systems on disease spread, and provide predictive analytics to identify intervention points for maximal efficacy/efficiency. Argonne develops and curates GIS information assets that can be used for resilience assessment and planning by decision makers and emergency response organizations.

Materials and chemistry capabilities: A broad array of materials and chemistry R&D, characterization, and manufacturing scale-up capabilities are available to develop alternate solutions for supplies of personal protective equipment, testing reagents and methodologies. Systems include polymer filtration media for masks, potential antiviral coatings, vaccine supply chain components, etc. Capabilities exist to develop alternative high-throughput approaches to synthesize vaccines, particularly alternatives to current incubation approaches.

Viral fate and transport: Argonne maintains capabilities and expertise to study fate and transport of SARS-CoV2 in the environmental, including in air in enclosed structures and wastewater/groundwater. This includes capabilities for modeling indoor air and particles/aerosols and viral traces in wastewater and groundwater.

Brookhaven National Laboratory

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National Synchrotron Light Source for protein structures: This DOE user facility at Brookhaven has unique capabilities to study the smallest crystals using specialized protein crystallography beamlines. A number of pharmaceutical companies are presently utilizing these capabilities as proprietary users, as well as academic general users. The NSLS-II is equipped to handle libraries of drug-based fragments and, using acoustic droplet ejection, druggable fragments can be rapidly screened for structure-based drug discovery using only nL droplets of samples. In addition, X-ray scattering combining small-angle (SAXS) to wide-angle (WAXS) regime can be used measure the solution-phase conformation of proteins, the aggregation state of protein clusters, and the interactions/packing between viral capsids. High-flux synchrotron microbeam experiments allows these measurements to be performed on small sample quantities.

Center for Functional Nanomaterials: The Center for Functional Nanomaterials (CFN) operates multiple microscopes for cryo-TEM holders based cryo-electron microscopy for imaging of biological macromolecules and one that has wide applications in the high-resolution study of viruses. A new cryo-Electron Microscope is being installed an additional approach for studying the novel coronavirus. A new SEM/FIB (scanning electron/focused ion beam) microscope has cryogenic automatic serial sectioning and image reconstruction capabilities, which are used to obtain tomographic images of frozen biological specimens with subcellular resolution, will be operational in summer 2020. CFN also operates a research cleanroom for fabrication of photonic, microfluidic, and simple electronic device architectures in 2D and 3D, which is useful for supporting biosensing/detection technologies. Additional capabilities available at CFN include 1) methods for fabricating ordered protein arrays screen of protein and antibody affinities in situ for use with both cryo-TEM and x-ray crystallography; 2) a video-rate atomic force microscope assess virus cell binding and binding inhibition and cell penetration process in real time; 3) Lab-based SAXS/WAXS capabilities provide quick measure of virus interaction with antibodies and viral envelope change in response to drug and/or vaccine candidates; 4) optical imaging and track single viruses using confocal and wide field fluorescence microscopy, along with development of advanced optical tags. The *CFN Theory & Computation Facility* offers suites of quantum chemistry and molecular mechanics software supported by high performance computing resources for molecular simulation

Computational Science: BNL has broad computational capabilities to support COVID-19 research, such as 1) established a high-throughput pipeline of open-source AI/machine learning (ML) tools and conventional physics-based simulations to accelerate drug and vaccine development and are screening 1.2 billion potential drug-like molecules for their ability to bind to known protein pockets on the SARS-nCoV-2 virus; 2) implementing a neural fingerprint method that can find and compare similar drug/chemical compounds quickly 3) developing an intelligent literature service that can extract drug, chemical, and biological information of relevance from the related literature.

*Other capabilities at Brookhaven: E*xpertise in studying the interaction of toxic agents with protective filtration and catalyst materials to understand capabilities for assays on proteins such as protease and to quantitate dissociation constants between proteins and ligands including drug candidates, other proteins, and DNA/RNA.

Fermi National Accelerator Laboratory

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High Throughput Computing: Working with the Open Science Grid (OSG) through their association with the COVID-19 High Performance Computing Consortium. Fermilab grid resources are available to receive HTC workflows which are denoted as Covid-19 research, utilizing donated/allocated and opportunistic cycles.

e-beam irradiation: The A2D2 facility is available for studies of irradiation sterilization with electron beams

Idaho National Laboratory

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Emergency response capabilities: INL has significant response team capability and experience for a wide variety of threats. All Hazards Analysis (AHA) and interdependencies analyses via experience in community resilience and medical supply chain resilience are available to contribute to assessments.

The biocontainment test facility at CITRC (infrastructure test range), integrated with our emergency response simulated Radiological Dispersal Device training event experiences are available for experimental testing of transmission/decontamination effectiveness evaluations.

INL's 890 mi^2 site provides numerous facilities for technology demonstration and testing useful for response, including a water security test bed and a wireless test bed, as well as radiological and nuclear facilities.

Manufacturing and Materials: INL has extensive advanced manufacturing capabilities that include additive and electric-field assisted sintering technologies. INL focuses on materials and manufacturing R&D for extreme environments, such as high temperatures or pressures, radiation, and corrosion. Further, INL has significant experience in developing instrumentation that functions in extreme environments. These capabilities are relevant for sensing and manufacturing challenges related to COVID-19.

Computing: INL is participating in the COVID-19 HPC Consortium. INL's hardware, with the recent addition of Sawtooth, provides significant capability for mid-range computing needs.

Lawrence Berkeley National Laboratory

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Advanced Light Source for structural biology: The Advanced Light Source, a DOE user facility, provides access to macromolecular crystallography capabilities, as well as high-throughput small-angle x-ray scattering (SAXS) structural characterization and soft x-ray tomography. SAXS can screen for interactions between viral proteins and potential diagnostic probes and candidate therapeutics. Soft x-ray tomography images organelles inside cells, allowing comparison between infected and uninfected cells.

National Energy Research Scientific Computing Center: NERSC is a DOE user facility that provides world-class supercomputing, data resources, and staff expertise to support simulation, data analysis, and AI/Machine Learning efforts. NERSC participates in the COVID-19 HPC Consortium as a resource provider and supports COVID-19 related research projects.

Computational algorithms and knowledge bases: Tools are available to build models of viral proteins, design antiviral compounds, create prioritized lists of viral and human targets and protein complexes, perform network analysis of interacting viral and human genes, and analyze viral variability. Extensive experience exists for aggregating various data types, their context, metadata, and provenance critical for supporting COV-19 response. Capabilities exist to create optimized models from crystallographic and cryo-EM data to guide the modeling of antiviral compounds.

CryoEM: CryoEM modalities can examine the structures of key viral proteins and their interactions with targeted molecules. Individual-particle electron tomography (IPET) and liquid-cell TEM can visualize an individual virus infecting a cell in 3D with nm resolution.

Molecular Foundry: The DOE's Molecular Foundry user facility has capabilities for developing specialized nanostructures that could form the basis for intrinsically antiviral surfaces and has developed equipment for testing the particle filtration efficiency of masks and respirators.

DOE Joint Genome Institute: JGI, a DOE user facility, performs large-scale sequencing of DNA and RNA libraries and computational genomic analyses, and could be employed for comparative genomics of coronaviruses from diverse host species and environments or SARS-CoV-2 genomes from diverse patient populations to investigate evolution, mutation frequency and constrained regions, and/or pathogenicity, as well as analyses of host-virus interactions, host microbiome changes with viral infection potentially accessible regions of surface proteins for immuno-targeting.

Virus contagion and risk models: Expertise in indoor environmental air quality and contaminant transport can be used to develop improved quantitative contagion and risk models using data from various indoor environments to improve estimates of transmissibility and aid in developing preventative strategies.

Other capabilities: 1) capacity to develop thousands of cDNA expression constructs, a prerequisite for structural biology and the development of antiviral agents; 2) modalities for detecting virus contamination on masks and surfaces; 3) microfluidic systems for large scale sample screening to support development of diagnostic probes; 4) synthetic biology-enabled production platforms and scale-up facilities for the production of antibodies, therapeutics, vaccines and small biologics relevant to the detection and treatment of COVID-19; 5) Transgenic/engineered mouse production to generate "humanized" mouse models for research studies of coronavirus infection; and 5) mass spectrometry and

time resolved x-ray imaging to characterize viruses and their microenvironments in droplets, which can help understand the survival of the virus in air and on surfaces.

Lawrence Livermore National Laboratory

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Medical Countermeasures Research and Development: Extensive computational and experimental capabilities and expertise exist for medical countermeasures, including 1) computational vaccine and therapeutic antibody design based on an artificial intelligence (AI) protein optimization pipeline, which can optimize binding of antibodies to the virus that causes COVID-19; 2) computational drug discovery pipeline with screening capability based on AI, molecular dynamics simulations and advanced HPC architectures to screen 100's of millions of small molecules against multiple SARS-CoV-2 targets; 3) extensive capabilities in protein structure modeling and prediction, including early structural predictions of the SARS-CoV2 spike protein, which were made available to the worldwide R&D community early in the pandemic before experimentally validated structures were available. LLNL is also heavily engaged in multiple partnerships to extend the national capabilities in drug development and discovery, including optimization of the safety and effectiveness of potential drug molecules discovered in large-scale COVID-19 computational screens.

Diagnostics Research and Development: LLNL has helped commercialize fluorescence in situ hybridization (FISH) assays, rapid PCR instrumentation, microdroplet PCR and DNA microarray technology in the past and maintain g capabilities in bioinformatics and bioengineering to support the detection of microbial species, including 1) developing a point of care genetic diagnostic system to detect the virus that causes COVID-19for medical professionals and emergency responders for rapid (~45 minutes) detection of COVID-19 and 2) developing an array system to rapidly all known/sequenced viruses, bacteria and fungi (>12,000 microbes), to include accurate detection of the virus that causes COVID-19. In a clinical diagnostic setting, this system can help assess co-infection with other viruses or bacteria to help better inform clinical care.

Engineering, and Material Science Capabilities: These capabilities have been deployed in the following areas: 1) Emergency room ventilators have been designed, prototyped, and licensed an emergency ventilation device (which a commercial partner is now producing) and extracorporeal membrane oxygenation (ECMO) systems are also being improved, and 2) development, evaluation and testing of sample collection swabs manufactured by 3D to support COVID-19 diagnostics needs.

Systems Analysis and Decision Support Tools: LLNL has extensive capabilities in systems analysis and decision support tools, such as models for providing a systematic and comprehensive evaluation of climate models and capabilities in uncertainty quantification in complex models of the nuclear weapons enterprise. These and other tools are being adapted and applied to epidemiological/systems models to support local and national COVID-19 decision-makers.

High Performance Computing: LLNL is home to powerful computers, several of which are capable of petascale computing (10^{15} floating point operations per second).

BSL-3 facility*:* LLNL maintains on-site a biosafety level 3 (BSL-3) facility, which is approved by CDC for work on 16 select and non-select risk group 3 agents. The SARS-CoV-2 virus responsible for COVID-19 disease is currently on-site, protocols for working with it in place and LLNL scientists are conduction R&D to support both medical countermeasures and diagnostics development. A full-service animal facility for rodents and other small species is available.

Los Alamos National Laboratory

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***Bioinformatics tools for infectious diseases*:** Bioinformatics tools developed at LANL quantify and help understand genomic aspects of several infectious diseases (COVID-19, HIV, flu, etc.) and are applicable to the study of coronavirus: point mutation, recombination, and placement of the current virus in the context of existing genomic knowledge of other coronaviruses. (**https://covid19.edgebioinformatics.org/#/home**)

Analysis of mutation rates: Phylogenomic analysis to refine the COVID mutation rate of virus and help define the infection rate.

Phylo-dynamics: Fusing genomic and epidemiological data using statistical and phylogenomic tools to answer epidemiologic-related questions.

Vaccine design. The Los Alamos mosaic design approach can help future-proof the population by designing mosaic vaccines against a wide range of coronavirus that exist in animal reservoirs (bats, snakes, etc.).

Epidemiological modeling: Building on epidemiological forecasting and modeling tools that were demonstrated successfully for influenza, Los Alamos is supporting decision makers with global characterization of spread prediction and stakeholder-driven scenarios for planning including re-openings and what supplies/countermeasures will be needed in specific locations. (https://covid-19.bsvgateway.org/)

Computational assessment of structural biology. 3D structures of the virus can be used to answer questions about what makes this virus different from the 2002-2003 SARS virus and assess whether recovered patients be re-infected.

New detection/characterization techniques*:* Provide new detection/characterization approaches with sequencing approaches via DTRA/CTR and Dept of State/BEP partners in Africa, Middle East, and former-Soviet Union.

Ventilator development :. Research capabilities for ventilator modifications that improve morbidity and mortality outcomes are using an instrumented experimental testbed integrated with multi-scale modeling. Current focus is analysis of aerosols and liquids in the reduction and removal of mucous from the lungs.

Other capabilities: *1)* Studies on structure 2)modeling of disease progression and prediction of spread via traditional and non-traditional datasets; 3) medical countermeasure development; 4) historical outbreak analysis for comparing to past outbreaks; 5) aid in evaluating containment or treatment methodologies; 6) FIE-related technical reach-back capabilities; 7) testing at BSL 1 and 2 labs; CLIA and ISO accredited labs; 7) database storage and analysis at multiple security levels; 8) within-host viral dynamics; 9) characterization of movement (persons, resources, etc.) and export control to compare previous events to current COVID event; 9) capability and tools to analyze recombinants; and 10)horizontal gene transfer database and tools.

National Energy Technology Laboratory

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Computational Modeling: High performance computing resources are available through NETL's **Joule2.0** HPC platform and enhanced through large data center capabilities at **WATT** which is housed in the Center for Data Analytics and Machine Learning (CDML). NETL maintains a strength in computational chemistry for the design and evaluation of functional materials and catalysts, chemical kinetics modeling/simulation, computational fluid dynamics with reactive chemistry, large dataset management and analyses, optimization, uncertainty quantification, and science-based AI and machine learning and HPC based capabilities for population dynamic pandemic model have been expanded.

Nanostructured carbon materials: Methodologies have been developed for producing high grade carbon materials (i.e., graphene, etc.) in various forms which have shown beneficial application in possible biosensor development. In addition, the team has developed concepts for antiviral coatings using covetic films and nanoparticles.

National Renewable Energy Laboratory

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Computational Modeling: High performance computing resources enabling detailed transport and chemical kinetics modeling/simulation, analysis of large datasets, optimization, uncertainty quantification, and expertise building AI based control strategies and surrogate models for complex phenomena. *Computational Biology expertise* in modeling protein-ligand and protein-protein interactions using molecular docking and molecular dynamics, enabling calculations of thermodynamics of binding, prediction of protein structures and function, understanding of mechanisms of enzymatic catalysis and kinetic/metabolic modeling. *Multi-scale modeling of biological complexes* from angstrom to micron scale and from pico to millisecond. Coarse grain model building and simulations for molecular systems such as virus capsid assembly, stability and dynamical behavior. *Computational fluid dynamics and rheology* potentially for mask design and flow characterization during sanitation for re-use.

Structural Biology: Crystal X-Ray Diffractometer latest Bruker generation w/10X beam brilliance comparable to synchrotron beamlines. *Crystallization Robot* capable of screening thousands of crystallization conditions for optimization. Expertise in biological x-ray crystallography and single particle reconstruction from Cryo-EM and EM data sets. *EPR, FTIR and stopped-flow UV-Vis* for protein analysis (e.g., binding kinetics).

Protein Production, Purification and Analysis: Surface Plasmon Resonance and Quartz Crystal Microbalance-Dissipation Systems to measure protein-protein interactions and protein-ligand binding (linked to computational methods for predictive models). *Ultra-high resolution MALDI-FTMS* for protein identification. *Bench to Pilot scale fermentation systems* including centrifugation, filtration, concentration and CIP (clean in place) equipment from 100L-9000L scale. *Protein purification* at throughput from microgram to 100g scale.

Analysis: Geospatial analysis; supply chain analysis; energy system modeling; economic impacts and resiliency analysis; and other data analytics to inform mitigation, preparedness, and recovery efforts.

Energy Resilience and Analysis: Modeling/Visualization of energy resilience strategies for critical systems and unique facilities (field hospitals, first responders, law enforcement, military ops). *Supply chain modeling and analysis* for essential energy system components.

Other Resources: Genome editing in non-model microorganisms using traditional and *CRISPR* based approaches. *Real time PCR instrumentation* and expertise, *HPSEC* for isolation and size characterization of viruses and viral particles. *Additive manufacturing* in the form of 3D printing, roll to roll capabilities and extensive partnerships.

Oak Ridge National Laboratory

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Spallation Neutron Source (SNS) and High Flux Isotope Reactor (HFIR): The SNS and HFIR DOE user facilities provide neutron crystallography and scattering capabilities for studying intact viruses and their individual molecular components, including investigating changes in virus particle structure in response to antiviral drugs and during activation and infection. The detailed structure of individual components of the virus particle can also be characterized, as well as the interaction of proteins with other substrates.

Epidemiological modeling: Approaches have been developed to computationally model disease spread across communities using geospatial and other data sources, artificial intelligence and supercomputing. The models can guide timely response and resource allocation for optimal disease management.

Oak Ridge Leadership Computing Facility (OLCF): OLCF currently supports COVID-19 projects ranging from gene expression analyses to molecular modeling for drug target discovery, to epidemiological modeling. In addition, OLCF is a founding member of the COVID-19 High Performance Computing Consortium. Examples of studies to date include 1) screening of 1.5 billion chemical compounds in 24 hours for binding to the SARS-CoV-2 main protease—the largest drug screening study ever undertaken on a supercomputer and 2) comparison of samples of lung fluid cells from COVID-19 patients with control patients to examine gene expression and co-expression patterns in the cells.

Center for Nanophase Materials Sciences (CNMS): A DOE user facility, CNMS, has capabilities to study biomaterials, including 1) a new cryogenic transmission electron microscope is being installed; and 2) atomic force microscopes (AFM) to study selective binding and provide a map of functional sites on either living or dead viruses. The CNMS nanofabrication facility has developed microfluidic and biosensor platforms that can be used for detecting and quantifying the presence of viruses in biological substrates.

Mass spectrometry (MS): MS-based techniques, with novel sampling modalities and high-performance computing, are being employed to both predict (docking simulations) and screen ligands that bind to/interfere with the main protease of the SARS CoV-2 virus, preventing its progression in host cells.

New testing modalities: Molecular diagnostic methods to amplify and quantify SARS-CoV-2 RNA in saliva have improved EUA methods, diversified supply chains, and mitigated interferences with detection. Synthetic single chain antibodies (nanobodies) are being used to detect viruses in clinical samples and to concentrate viral proteins and particles from environmental samples for sensitive, rapid (minutes) detection of viral proteins and antiviral antibodies using bio-layer interferometry.

Environmental fate and transport: Advanced aerosolization methods and innovative aerosol collection systems combined with automated particle analysis and testing, are used to enable simulations of dispersion, while multimodal microscopy and biophysical measurements enable studies of contact transfer and re-aerosolization.

Advanced Manufacturing (AM): Metal AM capabilities have been employed to rapidly manufacture injection mold tooling for producing reusable respirators and multi-well test plates. In this latter case, this tooling has allowed ThermoFisher to produce up to 10 million test kits per week. The Carbon Fiber Technology Facility at ORNL has been used to develop production of N95 materials, which have been

characterized at the CNMS. These technologies have allowed Cummins to produce enough material for over 1 million respirators per day.

Pacific Northwest National Laboratory

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Emerging infectious diseases: PNNL has a leased BSL-3 facility on the University of Washington campus to analyze SARS CoV-2 infected human clinical samples and viruses and has a CLIA-certified clinical specimen analysis laboratory to enable the analysis of patient specimens for diagnostic purposes and the objective analysis of new testing methods and instrumentation.

Omics capabilities: The Environmental Molecular Sciences Laboratory (a DOE/BER user facility) has capabilities to identify functional markers of host-pathogen interactions to understand pathogenicity and develop approaches for countermeasure and therapeutics. . These tools have been used to study samples from 2015 Ebola outbreak in Sierra Leone and to investigate the functional differences that make the highly pathogenic MERS virus more virulent than low pathogenic SARS virus. The Center for Host Response Infectious disease Signatures (CHRIS) is a collection of host responses to 23 strains across 6 viral families, including 3 major syndromes comprising of >11,000 data sets for in vitro and in vivo (mouse and human) samples. With this collection, machine learning/AI and advanced statistical/graph methods are being developed to perform multi-'omics analysis for biomarkers of disease severity and identification of therapeutic targets.

Minimizing spread: PNNL has developed and validated Public Health Actionable Assays for transfer to the Centers for Disease Control for deployment in the Laboratory Response Network to provide situational awareness to support decision-makers. PNNL has developed approaches to understand the persistence of pathogens in the environment and on surfaces, a capability that could be applied to answering questions about the persistence of SARS-CoV-2 , such as whether it transmits via fomites.

Training and response: PNNL has long-standing expertise in biosecurity and safety training for first responders, including of the Pacific Northwest Regional Technology Center, which benefits the Seattle-area first responder community. Other capabilities include biosurveillance and syndromic surveillance, and operations research.

Disease modeling and impact analysis tools: PNNL has several activities focused on the intersection of biosecurity and public health, with a broad array of tools developed for assistance in disease modeling and impact. https://www.pnnl.gov/biodefense-technologies

Supply Chain Modeling: PNNL's State Planning and Response Tool for Operational Strategies integrates disease transmission, hospital resource, medical supply chain, and mitigation modules to model and analyze the effects of a disease outbreak to facilitate resource management and planning. The impacts and effects of input assumptions across various response measures (e.g., media announcements, school closures, effectiveness/resource requirements of airport surveillance, etc.) help assess the potential efficacy of these measures against disease transmission and outbreak progression, along with associated implementation and operations/sustainment costs of such measures.

Machine Learning and AI: Machine learning approaches have been developed for prediction of longitudinal patient trajectories to better understand outcomes related to symptomatic patterns, socio demographic influencers, and identify subpopulations for enhanced screening. Submodular optimization for computing approximate solutions are being developed for the design of optimal intervention/vaccination strategies. AI models – natural language understanding, machine learning,

deep learning, and data analytics are being used to describe, predict and prescribe COVID-19 dynamics from open-source data.

Sandia National Laboratories

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Critical medical materials and manufacturing support: SNL is working with New Mexico-based small businesses to increase the availability of medical supplies, characterizing the performance of locally manufactured N95-like masks, and are assisting a local distillery to switch to making hand sanitizer. In partnership with the University of New Mexico Hospital and Presbyterian Hospital, Sandia is developing a kit to convert a CPAP machine into a ventilator.

Data analytics and decision support: SNL is customizing novel text and data mining tools to quickly ingest new incoming data to yield key information that can be passed on to decision makers for the COVID-19 response. For example, the Rapid Syndromic Validation Project (RSVP) collects syndromic data from hospitals, clinics, and other sources to allow public health officials to rapidly gather data about the disease in the absence of laboratory data and help prioritize distribution of resources to communities.

Risk Communication and Training: SNL provides biological risk awareness and risk mitigation training to global partners and has readily deployable expertise that can be used to deliver similar training to domestic and additional international partners. In addition, SNL has training modules for targeting the proper use of PPE, waste management, and other modules for Field biosecurity and biosafety for field and laboratory workers and emergency responders.

Inform and optimize sampling and decontamination efforts: SNL has extensive experience with sampling and decontamination chemistry and deployment for viral RNA such as SARS-COV-2, including studies of decontamination effectiveness, software decision support tools to enable real-time collection and contamination mapping, and reach back to companies using Sandia developed and licensed decontamination foam in use in Wuhan

Detection and Diagnostics: A portable rapid (20min) viral detection system has been developed based on a low-cost portable instrumentation. Previous studies with Zika indicated that--using Sandia's "QUASR" assay chemistry--viral RNA can be detected directly from clinical matrices without time-intensive RNA extraction. In addition, a panel of immunoassays are being developed to detect viral antigens and anti-SARS-CoV-2 antibodies produced in response to infection. Direct detection of viral RNA via QUASR RT-LAMP, combined with detection of host response to infection *via* SpinDx immunoassay, will enable diagnosis of COVID-19 at all stages of disease. Moreover, this combination of assay types would enable us to both positively identify SARS-CoV-2 and rule out influenza or other coronaviruses.

Targeted protein therapeutic candidates: Structure-based computational design is being used to develop therapeutic antibodies that neutralize SARS-CoV-2 and engineering them for enhanced immune-protective characteristics and efficient lung tissue penetration. Nanoparticles carrying therapeutic mRNA/siRNA are being evaluated for efficient delivery of these and other therapeutic cargos to the lung and liver. Surrogate coronavirus systems are being developed to study either the immune properties of the surface spike protein or the entry pathway of the virus that can aid in the development of field deployable diagnostics, novel vaccines, antibody therapeutics and/or novel countermeasure approaches using CRISPR-based gene regulation.

Tracking changes in SARS-CoV-2 Genomic Sequences: Changes in the SARS2 virus (COVID-19 agent) genomic and protein sequences are being studied to understand clinical outcomes and predicting future impacts of the virus. Genome and protein sequence analysis tools are being developed to provide enabling technology for monitoring SARS2 to support determination of 1) chains of transmission and 2) the functional consequences of sequence changes over outbreak progression, including effects on diagnostics.

Savannah River National Laboratory

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Facilities and capabilities for advanced manufacturing including modular chemical process intensification, robotics, advanced automation, process control, rapid fabrication of containment structures, and information technology systems, often operating in hazardous or remote environments. These capabilities have been used for the development and deployment of inspection technologies, control methodologies, novel instrumentation for detection, prototype air purification/handling systems, and optimization approaches of hardware and software platforms to deliver products in a rapid and distributed fashion to increase productivity, process agility, and safety performance. Some areas of expertise applicable to COVID-19 include decontamination/sterilization methods based on ozone, supercritical CO_2, UV and microwave irradiation, filter- and collection-technology utilizing electrostatic precipitation, and modeling/analysis of supply chain disruptions for test kits, PPE and other manufactured components.

Testing facilities for studies of chemical and spectral bioanalysis, genome/transcriptome profiling, microscopy, metabolome analysis, proteomics, and plant/microbe interactions. These facilities include tools for biomolecular preparation and purification for microbial and cell culturing, manipulation, sorting, and genetic engineering/synthetic biology.

Data analysis and AI capabilities used for modeling the fate and transport of aerosolized species in groundwater, wastewater and atmosphere for real-time decision making and risk analysis. Understanding of the relationships between viral characteristics, environmental factors, water chemistry, processing, genetic signals, viral inactivation and infection rates can be obtained.

Viricidal materials based on polymeric coatings, nano-structured particles, and advanced composite ceramics to reduce transmission and unintended exposure. These materials are relevant to advances and reuse of medical PPE, (e.g., gloves, gowns/aprons, masks, respirators and ventilator tubing) and a wide variety of other commonly used surfaces by providing virus inactivation through their high surface-contact area, highly active and stable nanoparticles, and micron architectures.

Emergency response facilities used as mobile detection platforms for screening and handling samples.

SLAC National Accelerator Laboratory

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Stanford Synchrotron Radiation Lightsource (SSRL)*:* At SSRL, a DOE user facility macromolecular x-ray crystallography capabilities are available to obtain high resolution structural insights into proteins, viruses, macromolecular machines and other macromolecules, including, two facilities specifically designed to study very small crystals, either at cryogenic or room temperature SSRL also has small- and wide-angle x-ray scattering (SAXS/WAXS) capabilities to study conformational changes of macromolecules in near-native solution states. They can be applied in time-resolved studies of virus particle maturation, to study ligand / fragment binding to proteins, aggregation states, and change in membrane curvature which is one of the key factors during viral infection. Finally, SSRL has extensive capabilities for the design and execution of in-situ X-ray experiments that characterize the physical phenomena in separation systems. For example, these capabilities were previously applied to study the transport and deposition of particulates in N95 filtration media.

Cryo-electron microscopy (cryo-EM): SLAC operates multiple instruments for cryo-electron microscopy and tomography (cryo-EM/ET), integrated within the SSRL operations. These instruments provide atomic-resolution capabilities that enable imaging of biochemically purified samples such as virus particles, membrane proteins, ion channels, protein machines, protein cages, protein-nucleic acid complexes, RNA, and their interaction with other macromolecules, antibodies and drugs. Supported by NIH, a dedicated national center for single particle cryoEM data collection is accessible to scientific users. In addition, there are associated BSL-2 laboratory facilities for tissue culture and sample preparation available to users needed prior to data collection. In addition, multiple imaging modalities spanning across different length scales is being established, including cryo-fluorescence super-resolution optical microscopy, cryo-focused-ion beam-scanning electron microscopy, and cryo-electron tomography of thick specimens for determining the 3-D structures of subcellular components' structure organizations *in situ* under normal and pathological conditions. Nano-X is a nanofabrication and metrology facility which operates a new cryo FIB/SEM (focused ion beam/scanning electron microscope) capable of serial sectioning and imaging for 3D imaging of frozen biological samples as well as cryo-TEM lamella preparation.

Linac Coherent Light Source (LCLS)**:** LCLS, a DOE user facility, has instruments for x-ray crystallography studies of viruses and their interaction with macromolecules and potential drug targets. Studies can be done at room temperature, at atmospheric pressure, and in native-like membrane environments with extremely small (few microns) crystals. Other instruments can provide structural and dynamic information on viruses in solution but at lower resolution. LCLS has unique capabilities to study protein dynamics from femtosecond to millisecond to second timescales using pump/probe and mix/inject technologies, enabling information to be obtained on areas such as the maturation of virus particles, all the way down to 'molecular movies' of protein dynamics, such as the catalytic molecular response driven by enzymatic reactions. Studies on SARS-CoV-2 on LCLS to date have provided high resolution, room temperature, damage-free structures of the main protease and its binding to various inhibitor drug targets that seek to mitigate replication of the virus. Ongoing studies are measuring the dynamics of viral protein interactions to study the detailed mechanisms of how the virus infects cells. LCLS has also been used to study the fibrous structure of N95 masks, providing single-fiber resolution that has been difficult to obtain otherwise.

***Joint Initiative for Metrology in Biology (JIMB)*:** JIMB convenes public-private-academic consortia to develop standards and control materials for biomolecular assays and collaborations are underway with CDC to identify gaps in availability of reference materials relevant to diagnostic tests for COVID-19.

Thomas Jefferson National Accelerator Facility National Accelerator Laboratory

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Computer Resources For COVID-19 Efforts: The Jefferson Lab operates compute clusters for the experimental and theory research programs at the laboratory. There are two technologies in use: traditional Intel CPU based clusters and GPUs. Two programs are making use of GPUs, the LQCD theory computation, and a nescient Machine Learning project. The scale of the resources available are: 1) LQCD 19g cluster 32 nodes each with 8 RTX 2080 GPUs; 2) Machine Learning - 3 nodes each with 4 Titan RTX GPUs; and 3) Conventional Intel(18p - 180 nodes, 68 cores, Intel Knight's Landing, 16p - 264 nodes, 64 cores, Intel Knight's Landing and Experimental Nuclear Physics cluster - equivalent of 7000 cores of AMD Rome).

Material Processing Resources: The Jefferson Lab operates two baking boxes with approximate size 3 ft x 3 ft x 7 ft (height) which are capable of reaching up to ~160C. WHO has indicated the SARS-CoV-2 virus is deactivated when held at a temperature of 75C for 30 minutes.

Electron Beam Irradiation: The Jefferson Lab has two electron beam facilities: UITF and LERF available for studies of irradiation sterilization with electron beams up to beam energy of 8 MeV and a dose of 3.02x106 kGy/min/L (H2O).