DOE National Laboratory Capabilities for COVID-19 Response

Executive Summary

This document summarizes the capabilities of U.S. Department of Energy (DOE) laboratories that may be responsive to the threats posed by COVID-19, from near-term responses to longer-term research and development (R&D) opportunities. It is based on a data call issued to DOE laboratory representatives on the National Virtual Biotechnology Laboratory (NVBL) 17-Laboratory Working Group and incorporates input received through September 1, 2020. This list will be updated regularly as laboratory representatives provide new information. These capabilities comprise diverse resources for experiment, computing, characterization, epidemiological modeling , and manufacturing, such as the following.

Molecular structural determination*: X-ray sources and neutron sources at DOE user facilities* provide macromolecular crystal structures at atomic-level resolution both for studies related to drug and vaccine development and for computational modeling. In addition, *cryo-electron microscopes* can be used to provide high-resolution structures of virus particles, proteins, and RNA and details of 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 (AI), molecular dynamics simulations, and modeling tools, combined with input from protein structure data, provide information to support research related to rapid surveys of existing drugs and development of antiviral agents and vaccines.

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

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

Other Resources

Facilities and capabilities for antiviral and vaccine design and production draw upon computational, synthetic, and production capabilities across several laboratories.

Capabilities in data analysis using computation-based tools, such as geospatial information systems, AI, 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.

Environmental fate and transport studies: Capabilities in aerosol and surface science, combined with computational modeling, are being used to assess airborne dispersion and transport of virus, transport of human-expelled droplets and aerosols, viral surface stability, and evaluation of virus population diversity in the environment.

Sophisticated emergency response capabilities include Biosafety Level (BSL) facilities at several laboratories capable of handling and studying the COV-19 virus and infected patient samples, a mobile emergency response laboratory with biosafety capabilities, and mobile detection platforms to screen samples. Several laboratories have Clinical Laboratory Improvement Amendments (CLIA) certification to analyze specimens for diagnostic purposes and have leveraged this experience to provide objective evaluations of new testing methods and instrumentation.

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Capabilities for COVID-19 Response by Laboratory

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 personal protective equipment (PPE), and prototyping capabilities.

Super-resolution bioimaging: Ames Laboratory bioimaging capabilities provide rapid, three-dimensional (3D) 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 Laboratory researchers are leading the development of open-source codes for quantum chemistry, particularly aimed at current and next-generation highperformance computers. These codes enable the treatment of large systems, capable of handling large biological molecules.

In addition to these resources, our contractor, Iowa State University, has many relevant capabilities, such as 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: The Argonne Leadership Computing Facility, a DOE user facility, supports the COVID-19 High Performance Computing Consortium and provides supercomputing resources for molecular modeling, bioinformatics, and epidemiology to accelerate the development of treatments and strategies to combat the COVID-19 pandemic. An AI-driven drug development pipeline is now part of collaborations with the University of Chicago (UChicago), AstraZeneca, Jannsen Pharmaceuticals, Chase Cancer Center, Memorial Sloan Kettering, and others. Deep learning, which is 1000× 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 National Institute of Allergic and Infectious Disease (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 UChicago, 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 biomedical research on bacterial infectious disease through the Pathosystems Resource Integration Center (PATRIC) (https://patricbrc.org/) and on viruses through the Virus Pathogen Database and Analysis Resource (ViPR) (https://www.viprbrc.org/). 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. The results can be used to downselect the number of compounds that go to crystallization trials. Complementing APS capabilities, the *Advanced Protein Characterization Facility* has specialized capabilities for gene cloning and for 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 capabilities in materials and chemistry R&D; characterization, including the *Center for Nanoscale Materials*; and manufacturing scale-up are available to develop alternate solutions for supplies of personal protective equipment (PPE) and 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 capability and expertise to study fate and transport of SARS-CoV-2 in the environment, including in air, 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. These capabilities are being utilized by a number of pharmaceutical companies as proprietary users and by general users from academia and other national laboratories. The NSLS-II is equipped to handle libraries of drug-based fragments; with acoustic droplet ejection, druggable fragments can be rapidly screened for structure-based drug discovery using only nanoliter droplets of samples. In addition, x-ray scattering combining small-angle (SAXS) to wide-angle (WAXS) regimes can be used to 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 allow these measurements to be performed on small sample quantities.

Cryo-EM: A new cryo-electron microscope co-located with NSLS-II has been commissioned and is being used to look at SARS-COV-2 proteins. It is open to proprietary and nonproprietary users.

Center for Functional Nanomaterials (CFN): This DOE user facility operates multiple microscopes for imaging of biological macromolecules and has wide applications in the high-resolution study of viruses. A new scanning electron/focused ion beam (SEM/FIB) microscope has cryogenic automatic serial sectioning and image reconstruction capabilities, which are used to obtain tomographic images of frozen biological specimens with subcellular resolution. 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 to screen for protein and antibody affinities in situ, for use with both cryo-TEM and x-ray crystallography; (2) a video-rate atomic force microscope for assessing virus cell binding and binding inhibition and cell penetration process in real time; (3) SAXS/WAXS capabilities that provide a quick measure of virus interaction with antibodies and viral envelope change in response to drug and/or vaccine candidates; and (4) optical imaging and tracking of single viruses using confocal and wide field fluorescence microscopy, along with development of advanced optical tags. The *CFN Theory and 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) a high-throughput pipeline of open-source AI/machine learning tools and conventional physics-based simulations to accelerate drug and vaccine development, which is currently screening 1.2 billion potential drug-like molecules for their ability to bind to known protein pockets on the SARS-nCoV-2 virus; (2) a neural fingerprint method to find and compare similar drug/chemical compounds quickly; and (3) an intelligent literature service that can extract drug, chemical, and biological information of relevance from the related literature.

Other capabilities at Brookhaven: Expertise 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. Viral transport modeling capabilities and x-ray imaging capabilities to look at effect of decontamination methods on, for example, N95 materials.

Fermi National Accelerator Laboratory

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High-Throughput Computing (HTC): Fermilab is working with the Open Science Grid (OSG) through its 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.

Electron-beam irradiation: The Accelerator Application Development and Demonstration (A2D2) facility is available for studies of irradiation sterilization with electron beams.

Idaho National Laboratory

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

The biocontainment test facility at INL's Critical Infrastructure Test Range Complex, in combination with our emergency response capabilities and our simulated radiological dispersal device training event experiences, is available for experimental testing of transmission/decontamination effectiveness evaluations.

INL's 890 mi^2 site provides numerous technology demonstration and testing facilities that can be useful for response evaluations, including a water security test bed, a wireless test bed, and 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 High Performance Computing 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 of infected and uninfected cells.

National Energy Research Scientific Computing Center (NERSC): This DOE user facility 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 High Performance Computing 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 COVID-19 response. Capabilities exist to create optimized models from crystallographic and cryo-electron microscopy (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 transmission EM (TEM) can visualize an individual virus infecting a cell in 3D with nanometer resolution.

Molecular Foundry: The Molecular Foundry, a DOE 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, JGI 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 and of host microbiome changes with viral infection in 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 preventive 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 (6) mass spectrometry and time resolved x-ray imaging to characterize viruses and their microenvironments in droplets, which can help build understanding of the survival of the virus in air and on surfaces.

Lawrence Livermore National Laboratory

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Medical Countermeasures R&D: Extensive computational and experimental capabilities and expertise exist at Lawrence Livermore National Laboratory (LLNL) to assist in the development of 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) a computational drug discovery pipeline with screening capability based on AI, molecular dynamics simulations, and advanced HPC architectures to screen hundreds of millions of small molecules against multiple SARS-CoV-2 targets; and (3) extensive capabilities in protein structure modeling and prediction, including early structural predictions of the SARS-CoV-2 spike protein, which were made available to the worldwide R&D community early in the pandemic before experimentally validated structures were available. LLNL has initiated multiple partnerships to extend national capabilities in drug development and discovery; partners include leading academic and government institutions as well as major pharmaceutical and IT companies. The capabilities of these partnerships include the optimization of the safety and effectiveness of potential drug molecules, which is being applied to COVID-19 therapeutics development.

Diagnostics R&D: LLNL has helped to commercialize fluorescence in situ hybridization (FISH) assays, rapid PCR instrumentation, microdroplet PCR, and DNA microarray technology in the past and maintains

extensive capabilities in bioinformatics and bioengineering to support the detection of microbial species. Current applications for COVID-19 include (1) development of a rapid point-of-care genetic diagnostic system and (2) application of a DNA microarray system to rapidly detect all known/sequenced viruses, bacteria, and fungi (>12,000 microbes), including SARS-CoV-2. 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 materials science capabilities: LLNL has extensive engineering and materials infrastructure to support our core mission. During the pandemic, these capabilities have been deployed for (1) designing, prototyping, and licensing of an emergency ventilation device (now being produced by a commercial partner), and (2) development, evaluation, and testing of sample collection swabs manufactured using 3D printing 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 a Biosafety Level 3 (BSL-3) facility on site; this facility 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 are in place, and LLNL scientists are conducting 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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Epidemiological modeling: Building on epidemiological forecasting and modeling tools that were demonstrated successfully for influenza, dengue, and other viruses, Los Alamos is supporting decision makers with global characterization of spread prediction and stakeholder-driven scenarios for planning, including reopenings and what supplies/countermeasures will be needed in specific locations. (https://covid-19.bsvgateway.org/)

Bioinformatics tools for infectious diseases: Bioinformatics tools developed at LANL quantify and help in understanding the 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 can be used to refine the COVID mutation rate of virus and help define the infection rate.

Phylo-dynamics: Fusing of genomic and epidemiological data using statistical and phylogenomic tools can help 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.).

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 can be reinfected.

New detection/characterization techniques: Los Alamos can provide new detection/characterization approaches with sequencing approaches via DTRA/Cooperative Threat Reduction and U.S. Department of State/Biosecurity Engagement Program partners in Africa, the Middle East, and the former Soviet Union.

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

Other capabilities: (1) Studies on structure; (2) modeling of disease progression and prediction of spread via traditional and nontraditional 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 reachback capabilities; (7) testing at BSL-1 and BSL-2 laboratories and CLIA- and ISO-accredited laboratories; (8) database storage and analysis at multiple security levels; (9) within-host viral dynamics; (10) characterization of movement (persons, resources, etc.) and export control to compare previous events to current COVID event; (11) capability and tools to analyze recombinants; and (12) horizontal gene transfer database and tools.

National Energy Technology Laboratory

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

Materials engineering and manufacturing: NETL's Functional Materials Team maintains dedicated facilities for the synthesis and characterization of nanomaterials, thin film systems, sorbents, polymers, and sensing materials. NETL's Structural Materials Team maintains specialized facilities for fabricating alloys at both bench and pre-pilot scales. For COVID-19 related projects, NETL's materials engineering facilities can be leveraged for development of antiviral coatings to prevent contamination of clothing and surfaces, fabrication of sensitive biosensors for detecting virus and drug levels in patients, and development of radiopaque and other materials used in a range of medical devices.

National Renewable Energy Laboratory

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Computational modeling: Assets include *high-performance computing resources* enabling detailed transport and chemical kinetics modeling/simulation, analysis of large datasets, optimization, uncertainty quantification, and expertise in 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 enables calculations of

thermodynamics of binding, prediction of protein structures and function, understanding of mechanisms of enzymatic catalysis and kinetic/metabolic modeling. Other capabilities include *multiscale 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; and *computational fluid dynamics and rheology* potentially for mask design and flow characterization during sanitation for reuse.

Structural biology: Resources include a *crystal x-ray diffractometer,* the latest Bruker generation with 10× beam brilliance comparable to synchrotron beamlines; a *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; and *electron paramagnetic resonance (EPR), Fourier transform infrared (FTIR), and stopped-flow UV-Vis* for protein analysis (e.g., binding kinetics).

Protein production, purification, and analysis: Resources include *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); *ultrahigh-resolution MALDI-FTMS* for protein identification; *bench to pilot-scale fermentation systems* including centrifugation, filtration, concentration, and CIP (clean in place) equipment from 100 L to 9000 L scale; and *protein purification* at throughput from microgram to 100 g scale.

Analysis: Resources span 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: Strengths include modeling/visualization of energy resilience strategies for critical systems and unique facilities (field hospitals, first responders, law enforcement, military operations), as well as *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; *high-performance size-exclusion chromatography (HPSEC)* for isolation and size characterization of viruses and viral particles; and *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): SNS and HFIR, both 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, a DOE user facility, 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 for studying biomaterials that include (1) a new cryogenic transmission electron microscope (TEM) now being installed; and (2) atomic force microscopes (AFMs) 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 the 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 more than 1 million respirators per day.

Pacific Northwest National Laboratory

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Emerging infectious diseases: Pacific Northwest National Laboratory (PNNL) has a leased BSL-3 facility on the University of Washington campus to analyze SARS CoV-2 infected human clinical samples and viruses. PNNL also 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 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 the 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 >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.

Viral fate and transport: PNNL has developed approaches to understand the persistence of pathogens in the environment and on surfaces, a capability that could be applied to the persistence of SARS-CoV-2, such as whether it transmits via fomites. PNNL is also studying the impacts of building ventilation on viral particle distribution and spread to understand transmission potential in the built environment.

Training and response: PNNL has long-standing expertise in biosecurity and safety training for first responders and operates the Northwest Regional Technology Center for Homeland Security, which benefits the Seattle-area first responder community.

Disease modeling and impact analysis tools: Several PNNL activities are focused at 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. Analysis of the impacts and effects of input assumptions across various response measures (media announcements, school closures, effectiveness/resource requirements of airport surveillance, etc.) helps in assessing 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, assess socio-demographic influencers, and identify subpopulations for enhanced screening. Submodular optimization for computing approximate solutions is 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 materials and manufacturing support: Leveraging the Center for Integrated Nanotechnologies (CINT), a DOE user facility, Sandia is using its advanced materials and additive manufacturing capabilities to address medical equipment and reagent supply-chain issues. We are working with New Mexico–based small businesses to increase the availability of medical supplies, characterizing the performance of locally manufactured N95-like masks, and assisting a local distillery in switching to making hand sanitizer. In partnership with the University of New Mexico Hospital and Presbyterian Hospital, Sandia has developed a kit to convert a CPAP machine into a ventilator (FDA approval pending). Sandia has also developed a low-cost, drive-up outdoor shelter that shields healthcare workers conducting COVID-19 testing and is offering the design and complete instruction manual at no charge.

Detection and diagnostics: Leveraging its engineering expertise and facilities such as its microfabrication facility (Microsystems Engineering, Science and Applications [MESA] Complex), Sandia has pioneered many detection and diagnostic systems that have been commercialized. These capabilities are being used to assist in developing point-of-care diagnostic devices and biosensors for rapid detection of SARS-CoV-2. Examples include (1) a multiplexed immunoassay device (SpinDx) that can be used for rapid

(<30 min) and sensitive detection of IgG and IgM from patient samples without sample preparation; (2) smart phone–based rapid detection of viral RNA using RT-LAMP chemistry; and (3) surface acoustic waveguide sensors for detection of RNA as well as antibodies. We are working with multiple companies for commercialization of Sandia innovations or assisting them with development of novel sensors. Sandia has developed an FDA-authorized test for COVID testing in its CLIA-registered laboratories (https://www.fda.gov/media/140544/download) that can be used as a reference test.

Decision support modeling and data analytics: Sandia has a successful record in developing modeling tools for decision support in the deployment of medical countermeasures and other resources. During the Ebola crisis in West Africa, Sandia modeled and analyzed Liberia's blood sample transport system, from treatment units to diagnostic laboratories; the Liberian Ministry of Health adopted the resulting recommendations to improve turnaround time and minimize exposure of uninfected patients. Sandia researchers are using their modeling expertise to help local and state public health officials in making decisions; examples include estimating resource demands for treating COVID-19 patients based on disease spread projections from epidemiological models, optimal distribution of limited medical resources and feasibility of national sharing strategies, testing and contact tracing needs for different levels of reopening, and designing vaccine distribution strategies.

Host-directed CRISPR/Cas9 therapeutics: Sandia has established a platform technology for creating deployable antiviral countermeasures using CRISPR-based technology. The antiviral will be able to be customized to respond to many different viruses, including coronavirus. The team is conducting animal testing with Ebola virus and plans to conduct in vitro tests with SARS-CoV-2 in the near future.

Risk communication and remote training delivery activities for relevant communities: Sandia 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.

Aerosol modeling and chambers: Using its fluid dynamics modeling and simulation codes and state-of-the-art aerosol experimental facilities, Sandia is conducting studies to understand viral transmission and interaction with surfaces.

Savannah River National Laboratory

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Facilities and capabilities for advanced manufacturing at Savannah River National Laboratory (SRNL) include robotics, advanced automation, process control, and rapid fabrication including additive manufacturing 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 including masks, design of containment structures, and optimization of hardware and software platforms to deliver products in a rapid and distributed fashion to increase productivity, process agility and safety performance.

Decontamination/sterilization methods are available; these methods are based on gamma irradiation and ozone, supercritical CO_2, UV, and microwave exposure and supported by filtration and collection technology utilizing electrostatic precipitation. SRNL can also provide modeling/analysis of supply chain disruptions applicable for test kits, personal protective equipment (PPE), and other manufactured components.

Testing facilities enable 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.

Model development for real-time decision making and risk analysis is another strength. Simulations for SARS-CoV-2 fate and transport in wastewater are combined with baseline data collection for sampling-to-qPCR-to-sequencing on a multiscale approach and establishing a "genomic stamp" for different treatment facilities. Work to determine the relationships between viral characteristics, environmental factors, water chemistry, processing, genetic signals, viral inactivation, and infection rates is underway. Risk models are also generated for environmental quality considerations and transport of a variety of unwanted species.

Data analysis, augmented reality, and AI capabilities can be used for real-time decision making and risk analysis. Machine learning is also deployed to assist with image analysis and interpretation for identifying defects in components and localizing abnormalities in the body.

Viricidal materials can be based on polymeric coatings, high surface area supported nano-catalysts, graphene, shape-engineered nanoparticles, and advanced composite ceramics to reduce transmission and unintended exposure. These materials are relevant to advances and potential reuse of medical PPE, (e.g., gloves, gowns/aprons, masks, respirators and ventilator tubing) and can be adapted for 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. These materials and associated analytical measurement capabilities also contribute to SRNL's detector development and characterization facilities.

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

SLAC National Accelerator Laboratory

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Stanford Synchrotron Radiation Lightsource (SSRL): At the 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. Resources include two facilities specifically designed to study very small crystals, at either 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. These capabilities 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 have been applied to study the transport and deposition of particulates in N95 filtration media.

Cryo-electron microscopy (cryo-EM): SLAC operates multiple instruments for cryo-EM and cryo-electron tomography (cryoET), integrated within 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, and RNA and of their interaction with other macromolecules, antibodies, and drugs. Supported by NIH, a dedicated national center for single-particle cryo-EM data collection is accessible to scientific users. In addition, associated BSL-2 laboratory facilities for tissue

culture and sample preparation are available to users if needed prior to data collection. Multiple imaging modalities spanning a range of length scales are being established for studying tissues and cells under normal and pathological conditions; these include cryo-fluorescence microscopy, cryo-focused-ion beam scanning electron microscopy (in collaboration with the Nano-X cleanroom facility), and cryo-ET for determining the 3D structures of subcellular components' structure organization in situ. Extensive data integration and processing across different imaging modalities using artificial intelligence algorithms are being developed for new structure discoveries.

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-micron) 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 time scales 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 at 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; 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

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Computer resources For COVID-19 efforts: The Thomas Jefferson National Accelerator Facility (Jefferson Lab) operates compute clusters for the experimental and theory research programs at the laboratory. Two technologies are in use: traditional Intel CPU-based clusters and GPUs. Two programs are making use of GPUs: the Lattice QCD (LQCD) theory computation, and a nescient machine learning project. The scale of the resources available is as follows: (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 Knights Landing and Experimental Nuclear Physics cluster - equivalent of 7000 cores of AMD Rome).

Materials processing resources: Jefferson Lab operates two baking boxes, approximately 3 ft $\times$ 3 ft $\times$ 7 ft (height), which can achieve ~160°C. The World Health Organization (WHO) has indicated that the SARS-CoV-2 virus is deactivated when held at a temperature of 75°C for 30 minutes.

Electron beam irradiation: Jefferson Lab has two electron beam facilities: the Upgrade Injector Test Facility and the Low Energy Recirculator Facility. Both are available for studies of irradiation sterilization with electron beams up to a beam energy of 8 MeV and a dose of 3.02×10^6 kGy/min/L (H_2O).