

# BRIEFER

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## Pathogen Early Warning: New Technologies and Approaches

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### INTRODUCTION

In early January 2020, scientists identified SARS-CoV-2 as a novel virus with similarities to bat coronaviruses and the SARS virus, which caused a deadly outbreak that spread to more than two dozen countries in 2003.<sup>1</sup> Scientists used metagenomic sequencing, an advanced form of genomic sequencing capable of identifying novel pathogens, to understand the nature of the virus as a significant public health threat, helping to inspire action and outbreak response measures.<sup>2</sup>

For the world to be ready for the next pathogen outbreak, it needs to bolster early warning via technologies like metagenomic sequencing, which represents one of the most important avenues for addressing future infectious disease outbreaks. An effective pathogen early warning system must be capable of rapidly detecting outbreaks of all known pathogens regardless of their

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<sup>1</sup>Fan Wu, Su Zhao, Bin Yu, Yan-Mei Chen, Wen Wang, Zhi-Gang Song, Yi Hu et al., "[A New Coronavirus Associated with Human Respiratory Disease in China](#)," *Nature* 579, no. 7798 (2020): 265-269; Eskild Petersen, Marion Koopmans, Unyeong Go, Davidson H. Hamer, Nicola Petrosillo, Francesco Castelli, Merete Storgaard, Sulien Al Khalili, and Lone Simonsen, "[Comparing SARS-CoV-2 with SARS-CoV and Influenza Pandemics](#)," *The Lancet Infectious Diseases* (2020).

<sup>2</sup> Ibid.

characteristics, and capable of detecting those new to human understanding. Such a system should also help estimate a pathogen's deadliness and rate of transmission. Taken together, early detection of an outbreak and its rapid characterization---when case numbers are low and normally more manageable---can make measures to halt spread much more effective. The knowledge produced can also give public health authorities confidence to take stronger, more specific actions.

The benefits are clear: If SARS-CoV-2 had been contained before escaping its country of origin, approximately four million deaths and counting could have been averted, including a mounting toll of more than 600,000 Americans.<sup>3</sup>

Even when a pathogen has spread relatively widely, early detection technologies properly applied allow finer-grained data on a pathogen's spread, enabling precision interventions in communities where transmission is actively occurring. Without strong early detection technologies, governments will need to intervene at larger scales, using measures like city and region-wide lockdowns, to contain a rapidly spreading disease. Many governments throughout the world have balked at these blunter interventions because of their economic and social costs, which often make them politically infeasible or difficult to enforce.

There are, however, a suite of technologies that can be integrated to create such an early warning system - described in this briefer. With these technologies the international community would be able to better address the full spectrum of biological threats the world might face. The technologies would enable rapid detection, characterization, and response for future infectious disease outbreaks.

The briefer is a companion to the July 2021 Council on Strategic Risks report *Toward A Global Pathogen Early Warning System: Building on the Landscape of Biosurveillance Today*, offering additional details regarding the technologies described in that report.<sup>4</sup> Further, the briefer describes how stakeholders, especially in the U.S. government, should invest in these technologies to move closer to a robust system able to handle the full spectrum of biological threats, including the emergence of the next novel pathogen and those with characteristics that have been such a challenge in the current pandemic, such as high degrees of transmissibility and pre-symptomatic or asymptomatic transmission.

This briefer begins with a brief overview of the pathogen early warning “layered detection” the authors have in mind. Afterwards, it provides a description of each type of technology, its current state of readiness, and proposed activities to move them toward being deployed at scale. The activities are organized so as to be easily referenced by those who are considering how to improve policies, private investments, philanthropic initiatives, and research and development programs.

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<sup>3</sup> World Health Organization, [WHO Coronavirus \(COVID-19\) Dashboard](#), accessed June 29, 2021; World Health Organization, [China COVID-19 Tracking](#), accessed June 29, 2021; U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, [COVID Data Tracker Weekly Review](#), June 25, 2021.

<sup>4</sup> [“Toward a Global Pathogen Early Warning System: Building on the Landscape of Biosurveillance Today,”](#) A product of the Janne E. Nolan Center on Strategic Weapons, an institute of the Council on Strategic Risks. Authors: Natasha Bajema, Bill Beaver, Christine Parthemore, Adejare Atanda, Joanne Horn, David Manheim, Daniel Regan, Sid Sharma, Jacob Swett, and Nikki Teran. Edited by Christine Parthemore and Francesco Femia. July 2021.

## TECHNOLOGIES AND APPROACHES

Metagenomic sequencing holds particularly high potential in terms of its contributions to a global pathogen early warning system. A central benefit is its ability to identify novel biological threats such as the next SARS-CoV-2, a capability largely lacking today.<sup>5</sup>

As a highly versatile technology, it has a number of other benefits, including one crucial to helping the world extricate itself from the current pandemic. Today, the instruments that enable metagenomic sequencing are essential tools in tracking mutation patterns of SARS-CoV-2. They were used to identify the B.1.1.7 variant (Alpha variant), in the United Kingdom, and the B.1.617.2 variant (Delta variant) first identified in India, both of which are significantly more transmissible than other forms of the virus.<sup>6</sup> Reflecting its promise, in the United States the Biden administration plans to invest \$200 million in related technology and another \$1.75 billion as part of the American Rescue Plan Act of 2021, potentially laying the foundation for a future, much more effective pathogen early warning system.<sup>7</sup>

In the near term, clinicians, epidemiologists and others should use metagenomic sequencing in conjunction with other tools. An example of how this would look: After clinicians or public health authorities detect a novel pathogen using metagenomic sequencing, they should then make use of less expensive, immediately scalable tests that can further help gather information on a pathogen's rate of transmission by rapidly diagnosing active cases (point-of-person detection) and detecting past cases (serological detection). Taken together, the list of technologies below can aid in creating a layered defense against biological threats regardless of the pathogen's characteristics or origin (i.e., whether they arise by nature, accident, or deliberate acts). They include approaches to directly detecting pathogens as well as detecting and understanding signals of their presence (e.g., physiological changes in people or changing patterns of activities).

- Metagenomic sequencing
- Massively multiplexed detection
- Environmental detection
- Serological detection
- Non-invasive detection, including wearables and volatolomics
- Rapid, scalable, point-of-person tests
- Digital detection of pathogens

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<sup>5</sup> Chaolin Huang, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, Li Zhang et al., "[Clinical Features of Patients Infected with 2019 Novel Coronavirus In Wuhan, China](#)," *The Lancet* 395, no. 10223 (2020): 497-506; Roujian Lu, Xiang Zhao, Juan Li, Peihua Niu, Bo Yang, Honglong Wu, Wenling Wang et al., "[Genomic Characterisation and Epidemiology of 2019 Novel Coronavirus: Implications For Virus Origins And Receptor Binding](#)," *The Lancet* 395, no. 10224 (2020), p. 565-574.

<sup>6</sup> U.S. Centers for Disease Control and Prevention, "[What is Genomic Surveillance](#)," accessed June 25, 2021; William Beaver, "[New SARS-CoV-2 Strain in the United States](#)," Council on Strategic Risks, December 30, 2020; "[How the Delta Variant Took Over](#)," *Wired*, June 21, 2021.

<sup>7</sup> Carl Zimmer and Noah Weiland, "[CDC Announces \\$200 Million 'Down Payment' to Track Virus Variants](#)," *The New York Times*, February 17, 2021; White House, "[Fact Sheet: Biden Administration Announces \\$1.7 Billion Investment to Fight COVID-19 Variants](#)," Statements and Releases, April 16, 2021.

Below, we provide short descriptions for the most promising technological areas together with proposed research, development, and deployment activities that can be undertaken starting today. We have organized the activities to align with the roles specific U.S. actors and agencies have in developing and advancing technologies, as follows:

**1. Ready for Procurement and Scaling.** A wide variety of implementing organizations should be involved with activities described below in procurement and scaling, from the Centers of Disease Control and Prevention (CDC), to the U.S. Department of Defense (DoD), to state-level public health departments.

**2. Advanced Development, Testing, and Evaluation.** U.S. government organizations that generally conduct this type of activity include the Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense (JPEO- CBRND) within the DoD and the Biomedical Advanced Research and Development Authority (BARDA).

**3. Early-Stage Research through Advanced Technology Development.** Organizations that generally conduct and oversee early-stage research through advanced technology development include: the Joint Science and Technology Office (JSTO) within the Defense Threat Reduction Agency (DTRA); BARDA's DRIVE (Division of Research, Innovation, and Ventures) program ; the National Institute of Allergies and Infectious Disease (NIAID); the National Institute of Health more broadly, including the National Human Genome Research Institute; and the Department of Energy's National Labs.

**4. High-Risk, High-Payoff Research.** The Defense Advanced Research Projects Agency (DARPA), the proposed Advanced Research Projects Agency for Health (ARPA-H), and the Intelligence Advanced Research Projects Activity (IARPA) are designed for conducting high-risk, high payoff research.

The recommendations that follow are informed by the expertise of the authors, expert interviews, and literature reviews on each of the pathogen detection approaches.

### *Metagenomic Sequencing*

Metagenomic sequencing is an all-purpose detection technology that could form the cornerstone of the world's pathogen early warning system, as described above. Its versatility comes from the fact that it identifies any pathogen, whether a virus, bacterium, fungus, or parasite, using their most fundamental aspect: the DNA or RNA present in all known organisms.<sup>8</sup> Additionally, metagenomic sequencing does so at a massive scale: it can spot and analyze millions of fragments of DNA or RNA in the same test. These characteristics allow for a single sample to be tested for any pathogen, whether known or novel, far exceeding the capabilities of diagnostics in

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<sup>8</sup> Ellen C. Carbo, Igor A. Sidorov, Jessika C. Zevenhoven-Dobbe, Eric J. Snijder, Eric C. Claas, Jeroen FJ Laros, Aloys CM Kroes, and Jutte JC de Vries, "[Coronavirus Discovery by Metagenomic Sequencing: A Tool for Pandemic Preparedness](#)," *Journal of Clinical Virology* 131 (2020): 104594.

general use today.<sup>9</sup> The metagenomic sequencing approach has developed into a far more capable form of genomic sequencing, which generally tests a sample for a single, known pathogen when used for early detection. In addition to discovering novel pathogens its capabilities include:<sup>10</sup>

- Detecting newly-emerged pathogens through being rapidly reconfigurable to target specific nucleic-acid sequences.
- Detecting unknown/unsuspected infections, such as those that are spreading pre-symptomatically, e.g., HIV.
- Tracking viral changes (e.g., variants).
- Distinguishing between co-infections.
- Estimating the origin of a virus by looking at the changes to its genetic material over time (phylogenetic analysis).
- Detecting and attributing engineering of pathogens, e.g., those that have undergone gain-of-function experiments or are intentionally developed for use as weapons.
- Enabling the design of diagnostic tests based on the mRNA or DNA of an organism.
- Enabling design of vaccines (e.g., mRNA).

However, metagenomic sequencing may require significant investment and iteration to realize its promise in a clinical setting, (i.e., at point of care) and much more research and development for its application in other settings. A particularly high priority is developing new means of sample acquisition, preparation, and analysis to continue driving down cost and complexity of operation.

### Next Steps

#### Ready for Procurement and Scaling

- Expand the expertise and infrastructure for metagenomic sequencing, bioinformatics, and data-sharing.
- Build clinical protocols for complex cases and develop processes that allow for rapid scaling of sequencing when needed.
- Modify Clinical Laboratory Improvement Amendments (CLIA) regulatory standards to allow for the reporting of genomic findings by public health labs to health care providers.
- Tightly control access to sequences of dangerous pathogens or information that can be used to engineer viruses for malicious purposes.

#### Advanced Development, Testing and Evaluation

- Improve efficiency and accuracy of bioinformatic pipelines for metagenomic pathogen detection, with algorithms that can alert users of novel pathogens.
- Pilot integration of clinical and sentinel metagenomics within a surveillance architecture. For example, sequence respiratory sputum samples for patients with pneumonia of unknown origin or a voluntary group of high contact individuals (e.g., healthcare

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<sup>9</sup> Steve Miller, Samia N. Naccache, Erik Samayoa, Kevin Messacar, Shaun Arevalo, Scot Federman, Doug Stryke, et al., "[Laboratory Validation Of A Clinical Metagenomic Sequencing Assay For Pathogen Detection In Cerebrospinal Fluid](#)," *Genome Research* 29, no. 5 (2019): 831-842.

<sup>10</sup> Katrina L. Kalantar, Tiago Carvalho, Charles FA de Bourcy, Boris Dimitrov, Greg Dingle, Rebecca Egger, Julie Han et al., "[Idseq—an Open Source Cloud-based Pipeline and Analysis Service for Metagenomic Pathogen Detection and Monitoring](#)," *GigaScience* 9, no. 10 (2020): g11111.

workers, grocery-store clerks). This list should expand to include those who interact with high-risk individuals or themselves are at high risk, such as technicians in BSL-4 labs, and also frequent travellers.

- Trial metagenomics as a front-line, broad-spectrum diagnostic with rapid anti-microbial resistance detection capabilities.

### **Early-Stage Research through Advanced Technology Development**

- Improve and integrate sample and library preparation methods on sequencing instruments to reduce hands-on time and risk of contamination while also increasing reliability.
- Improve methods to increase specificity for relevant genomic material (e.g., pathogens, host transcriptomes) but maintain sequencing's agnosticism. Such methods could include pathogen enrichment, host depletion, and selective sequencing. An example of a selective sequencing approach is ReadUntil from Oxford Nanopore.<sup>11</sup>
- Develop fast and secure cloud-based bioinformatic pipelines for metagenomic pathogen detection.
- Research methods to ensure that databases of genomic sequences are free from tampering and protected from cyber attacks such as data poisoning.
- Develop metagenomic sequencing approaches that also integrate detection of engineered pathogens and attribute the source of the engineering. An example of a related effort is IARPA's FELIX program, whose goal is agnostic detection of engineered organisms.<sup>12</sup>

### **High-Risk, High-Payoff Research (i.e., Moonshots)**

- Develop new instruments that require reduced or simplified reagents and run on push-button and/or automated sequencers in a variety of clinical settings, including those that are low-resource.
- Develop new instruments with the above characteristics that are also handheld.

### ***Massively Multiplexed Detection***

Massively multiplexed detection encompasses a group of technologies that are capable of testing all known pathogens (i.e., a pan-pathogen panel) at once based on a single sample and a single test; they can even detect some emerging or engineered pathogens based on genetic similarities with known biological threats.<sup>13</sup> In comparison to metagenomic sequencing, massively multiplexed approaches have similar advantages over the current dominant paradigm in pathogen detection technology (i.e., PCR-based diagnostics) but are not as capable at detecting novel pathogens. There are already proofs of concept for massively multiplexed approaches, especially those that use the genome editing tool clustered regularly interspaced short palindromic repeats, better known as CRISPR.

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<sup>11</sup>[“Towards Real-time Targeting, Enrichment, or Other Sampling on Nanopore Sequencing Devices, Rather Than in the Sample Prep: Adaptive Sampling for Selective Nanopore Sequencing,”](#) Oxford Nanopore Technologies, accessed July 26, 2020.

<sup>12</sup> U.S. Office of the Director of National Intelligence, [Finding Engineering-Linked Indicators](#), solicitation accessed June 30, 2021.

<sup>13</sup> Defense Advanced Research Projects Agency, Department of Defense, [Special Notice \(SN\) DARPA-SN-20-12: DIGET Proposers Day](#), 2019; David Wang, Anatoly Urisman, Yu-Tsueng Liu, Michael Springer, Thomas G. Ksiazek, Dean D. Erdman, Elaine R. Mardis et al, "Viral discovery and sequence recovery using DNA microarrays," *PLoS Biol* 1, no. 2 (2003): e2.

Massively multiplexed detection can be made portable, user-friendly and inexpensive with the help of devices that automate the more cumbersome aspects of preparing and testing samples (lab-on-a-chip technology). Besides CRISPR massively multiplexed approaches, there are those that are microarray-based that deserve attention.<sup>14</sup> An early example of research in this area includes the Virochip.<sup>15</sup> Bill Gates, in a January 2021 blog post, called for mega-diagnostic platforms that can test for up to twenty percent of the global population each week in a health emergency.<sup>16</sup> These inexpensive, broad-spectrum, rapid methods could help make this goal a reality in the near term.

### Next Steps

#### Ready for Procurement and/or Scaling

- Plan for sustained government funding to purchase new devices and provide training.

#### Advanced Development, Testing and Evaluation

- Pilot projects using prototypes.
- Transition the DARPA Detect It with Gene Editing Technologies (DIGET) Program to the Department of Defense's Chemical and Biological Defense Program (CBDP) or another partner such as BARDA and diversify the number of collaborators.
- Begin developing manufacturing infrastructure to mass produce CRISPR-based massively multiplexed diagnostics.

#### Early-Stage Research through Advanced Technology Development

- Develop a variety of novel, massively multiplexed approaches, including multiplexing both in the direction of testing for many pathogens and multiplexing to test many individuals' samples at once.

### *Environmental Detection*

During the SARS-CoV-2 pandemic, public health authorities began examining wastewater for signs of SARS-CoV-2 in select communities.<sup>17</sup> Wastewater detection is one of a family of approaches that relies on environmental samples. Other examples of this approach include: collecting samples from waterways, which accumulate genetic material of local organisms; sampling the air at event venues or other locations such as airports, military installations, the White House, or any places that may be targets of a biological attack; and testing organisms that naturally sample the environment, such as mosquitos.

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<sup>14</sup> Lin Wu, P. Mickey Williams, and Walter H. Koch, "[Clinical Applications of Microarray-based Diagnostic Tests](#)," *Biotechniques* 39, no. 4S (2005): S557-S582.

<sup>15</sup> Eunice C. Chen, Steve A. Miller, Joseph L. DeRisi, and Charles Y. Chiu, "[Using a Pan-viral Microarray Assay \(Virochip\) to Screen Clinical Samples for Viral Pathogens](#)," *Journal of Visualized Experiments: JoVE* 50 (2011).

<sup>16</sup> "[The Year Global Health Went Local](#)," GatesNotes, The Blog of Bill Gates, accessed July 1, 2021.

<sup>17</sup> Jordan Peccia, Alessandro Zulli, Doug E. Brackney, Nathan D. Grubaugh, Edward H. Kaplan, Arnau Casanovas-Massana, Albert I. Ko, et al., "[Measurement of Sars-CoV-2 Rna in Wastewater Tracks Community Infection Dynamics](#)," *Nature Biotechnology* 38, no. 10 (2020): 1164-1167; Yakir Berchenko, Yossi Manor, Laurence S. Freedman, Ehud Kaliner, Itamar Grotto, Ella Mendelson, and Amit Huppert, "[Estimation of Polio Infection Prevalence from Environmental Surveillance Data](#)," *Science Translational Medicine* 9, no. 383 (2017).

The wastewater-based detection for SARS-CoV-2 currently being done across the world helps scientists estimate the spread of the virus in a specific community based on the amount of genetic material found in samples; it can be a more accurate means of tracking infections because it picks up asymptomatic and presymptomatic cases that are less likely to have been tested or diagnosed by a doctor. As a measure to begin characterizing the rapidity of a pathogen's spread, wastewater sequencing could be used early in an infectious disease outbreak to gain a general understanding of pathogen reproduction rates and locations where it is spreading. If wastewater sequencing of SARS-CoV-2 was immediately implemented earlier in the pandemic, countries all over the world could have had much better insight into when the pathogen entered the country and necessary interventions could have been targeted at specific communities.

When environmental detection has been conducted, it has been primarily pathogen-specific - targeted at an individual microorganism such as SARS-CoV-2 or pathogens on the government's list of select agents. Though essential immediately after the detection of an outbreak or for tracking known pathogen threats, these approaches offer significant additional benefits that the international community should pursue. An ideal system for environmental detection would be broadly deployed, automated, and able to identify every single known pathogen. In addition, it would be capable of noticing or setting off an alarm in case of the presence of any known or unknown pathogens whose genetic presence is exponentially increasing in samples.<sup>18</sup> Metagenomic sequencing and massively multiplexed detection are both approaches that should be applied as part of environmental detection.

### **Next Steps**

#### **Ready for Procurement and/or Scaling**

- Promote wastewater sequencing for specific pathogens of interest.
- Sustain vector-based detection targeted at pathogen-carrying organisms such as mosquitoes, which naturally collect samples from organisms in an environment.

#### **Early-Stage Research through Advanced Technology Development**

- Develop protocols and sample collection methods for metagenomic sequencing of wastewater and waterways.
- Experiment with methods for identifying novel pathogens through environmental metagenomic sequencing.
- Advance methods for collection and processing of samples in specific environments (e.g., water, air, agriculture, and surfaces).
- Create applications for environmental sequencing outside of early detection (e.g., detecting antimicrobial resistance detection) in a community.
- Pilot an environmental surveillance system using massively multiplexed approaches such as CRISPR in municipal sewage and wastewater.

#### **High-Risk, High-Payoff Research (i.e., Moonshots)**

- Build automated environmental metagenomic sequencing detection devices and workflows that connect to a centralized server and have similar capabilities to the clinical metagenomic sequencing described above, including the ability to detect all known

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<sup>18</sup> Kevin Esvelt, conversation with authors, July 11, 2021.

pathogens and those that are novel; environmental metagenomic sequencing is expensive at the moment but also a relatively proven technology with high payoff.

### *Serological Detection*

Serological detection (i.e., methods that detect signs of human immune responses) can provide another route to pathogen detection, including for presymptomatic spread, latent infections, and potential zoonotic threats. It can be used as a means to better understand the transmissibility of a pathogen by testing those who may have already been infected and who may have recovered. It is also essential for developing many therapeutics.

Serological detection methods test for the presence of antibodies. Normally, technicians only search for a few antibodies at a time in clinical and surveillance settings. However, with technological advances, scientists have devised methods that screen for multiple antibodies for a range of pathogens.<sup>19</sup> Serological detection is helpful in particular when there is presymptomatic spread or past exposure to a pathogen. It is not as effective in detecting the pathogen's presence in the early stages of an infection in an individual, given that it takes time for the immune system to produce antibodies.

A group of scientists have proposed the establishment of a Global Immunological Observatory to harness the early detection potential of the immune response.<sup>20</sup> They envisage taking advantage of routine collection of blood samples from across the globe to test for multiple antibodies. This could provide a powerful means to detect outbreaks of certain viruses.

Serological detection may enable safer and more effective forms of surveillance of potential zoonotic pathogens. Instead of seeking out all existing pathogens with the potential of transmissibility between humans, the search space can be constrained significantly to those pathogens that have already infected humans. This can reduce reliance on virus hunting, which exposes scientists themselves to pathogens that could start a pandemic. There are several possible methods that are high potential but require additional research and development before implementation as it is difficult to detect antibodies for novel pathogens, including more sophisticated serological techniques based on massive arrays of pseudo-random peptides. Coupled with machine learning, these methods have demonstrated promise for producing unique serological signatures across infections for known pathogens. Extending this capability to novel pathogens coupled with host-based immune profiling would allow for pre-scaled capacity to conduct serology for measuring prevalence during an outbreak and for constant monitoring of sentinel populations for asymptomatic infections.

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<sup>19</sup>George J. Xu, Tomasz Kula, Qikai Xu, Mamie Z. Li, Suzanne D. Vernon, Thumbi Ndung'u, Kiat Ruxrungtham, et al., "[Comprehensive Serological Profiling Of Human Populations Using A Synthetic Human Virome](#)," *Science* 348, no. 6239 (2015).

<sup>20</sup>Michael J. Mina, C. Jessica E. Metcalf, Adrian B. McDermott, Daniel C. Douek, Jeremy Farrar, and Bryan T. Grenfell, "[Science Forum: A Global Immunological Observatory To Meet A Time Of Pandemics](#)," *Elife* 9 (2020): e58989.

## Next Steps

### Ready for Procurement and/or Scaling

- Create immunological observatories that test a representative sample of the global population for antibodies and pathogen sequences to detect outbreaks that are spreading pre-symptomatically or asymptotically.
- Conduct serological testing of lab workers to better understand lab safety risks and past near misses, i.e., situations where lab workers were infected but a pandemic did not result.

### Early-Stage Research through Advanced Technology Development

- Develop methods of serological detection of emerging viruses for later application to at-risk populations.
- Advance sophisticated serological techniques based on massive arrays of pseudo-random peptides.
- Research host-based immunoprofiling to enable detection of novel pathogens.

### High-Risk, High-Payoff Research (i.e., Moonshots)

- Gather data to establish the baseline immunological profile of the global population.

### *Non-Invasive Detection, Including Wearables and Volatolomics*

Wearable fitness tracking and health tracking devices have the potential to be used for very early detection of an infection in an individual. They may also be helpful for detecting asymptomatic or latent infections. Recent research has found that these devices, already in widespread use around the world, can be used to detect signs of some infections before noticeable symptoms appear.<sup>21</sup> They function by establishing baseline readings for individuals, and when changes to heart rate, sleep, activity, etc. could correlate with an infection, the device sends an alert.

Wearables for early detection have seen active experimentation, research and even deployment during the COVID-19 pandemic.<sup>22</sup> For example, the NBA, NASCAR and U.S. defense forces used Oura Rings to detect signs of COVID-19 before the appearance of noticeable symptoms, relying on fluctuations in the wearer's skin temperature. The technology has potential for aiding in early detection of infectious disease outbreaks, including those caused by lab accidents. Lab workers handling the most dangerous pathogens should use these devices as an additional warning system for an accidental infection that could begin a pandemic. Another potential use case would be for militaries to equip these devices for ensuring the general readiness and fitness of personnel while also providing early warning capability against biological weapons. An example of an application could be presymptomatic detection of exposure to weaponized

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<sup>21</sup> H. Ceren Ates., Ali K. Yetisen, Firat Güder, and Can Dincer, "[Wearable Devices for the Detection Of Covid-19](#)," *Nature Electronics* 4, no. 1 (2021): 13-14; Emily A. Vogels, "[About One-in-five Americans Use A Smart Watch or Fitness Tracker](#)," *Pew Research Center*, January 9, 2020.

<sup>22</sup> Robert P. Hirten, Matteo Danieletto, Lewis Tomalin, Katie Hyewon Choi, Micol Zweig, Eddy Golden, Sparshdeep Kaur, et al., "[Use of Physiological Data from a Wearable Device to Identify SARS-CoV-2 Infection and Symptoms and Predict COVID-19 Diagnosis: Observational Study](#)," *Journal of Medical Internet Research* 23, no. 2 (2021): e26107; "[Your Apple Watch Could Soon Tell You If You've Got Coronavirus](#)," *Wired*, March, 9, 2020.

smallpox, which takes up to two weeks for symptoms to appear. In the longer term, aggregated and anonymized data from these devices could be used as a data stream that feeds into a global early warning system.

The main challenge with wearable-based detection is accuracy. There are high false-positive rates. A possible solution is to collect and integrate more signals. For example, integrating devices tracking perspiration, gait, voice tone, or respiratory rate could be explored, or volatolomics, which relies on pathogen-caused chemical reactions that result in a detectable byproduct such as a gas. Electronic noses and gas sensors are further examples of non-invasive approaches to research.<sup>23</sup> An additional approach is to integrate synthetic biology sensors into masks.<sup>24</sup>

As an additional layer for pathogen early warning, these signals could be aggregated and analyzed for anomalies in specific geographic areas. When anomalies are detected, public health officials could then conduct community testing using metagenomic or CRISPR-based massively multiplexed testing.

### **Next Steps**

#### **Ready for Procurement and/or Scaling**

- Drive use of consumer wearables as an early detection approach for SARS-CoV-2 and influenza among high-risk groups and integrate warnings that urge users to pursue that then leads to pathogen-specific testing in medical facilities.

#### **Advanced Development, Testing and Evaluation**

- Deploy health trackers for researchers at BSL-3/4 labs, together with pathogen-specific diagnostics.
- Deploy wearables by the military as an early detection technology to detect and quickly respond to any local outbreaks of respiratory infections, with the goal of drastically reducing cases on a military base over a year.
- Conduct large-scale studies on pre-symptomatic detection of respiratory infections, using various wearables.
- Develop and publish anonymized, large-scale, publicly available datasets that will allow experimentation with the software backbone to increase detection accuracy and timeliness.

#### **Early-Stage Research through Advanced Technology Development**

- Based on lessons from commercial wearables, conduct research and development on devices specifically made for presymptomatic detection of a pathogen to be used at BSL-3 and 4 labs.

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<sup>23</sup> Susana ICJ Palma, Ana P. Tragedo, Ana R. Porteira, Maria J. Frias, Hugo Gamboa, and Ana CA Roque. "[Machine Learning for the Meta-analyses of Microbial Pathogens' Volatile Signatures](#)," *Scientific Reports* 8, no. 1 (2018): 1-15.

<sup>24</sup> Peter Q. Nguyen, Luis R. Soenksen, Nina M. Donghia, Nicolaas M. Angenent-Mari, Helena de Puig, Ally Huang, Rose Lee et al, "[Wearable Materials with Embedded Synthetic Biology Sensors for Biomolecule Detection](#)," *Nature Biotechnology* (2021): 1-9.

- Explore other broadly deployed “internet-of-things” devices such as speakers or smart thermometers for tracking outbreaks of infectious disease in communities.
- Experiment with datasets to develop anomaly detection algorithms that can spot outbreaks within a community.
- Research non-invasive volatolomics that can detect a wide variety of biological threats.

### **High-Risk, High-Payoff Research (i.e., Moonshots)**

- Detect and flag any infection, especially while an individual is presymptomatic or asymptomatic, while integrating a variety of inputs from non-invasive detection devices.

### *Rapid, Scalable, Point-of-Person Tests*

Point-of-person tests are cheap, easy to use, and can be conducted by a layperson or in clinical settings. Late in the pandemic, at-home testing for SARS-CoV-2 has become much more widespread. Future outbreak early detection systems should rely heavily on technologies like metagenomic sequencing that can accurately detect any biological threat. However, today’s point-of-person detection technologies that test for fewer, specific pathogens will still play a fundamental role. In the long-term, technology developers should aim for point-of-person tests that are pathogen agnostic like metagenomic sequencing while also remaining rapid, accurate, and scalable.

Health care providers have been lukewarm in their support of patients testing themselves at home using rapid diagnostic tests.<sup>25</sup> With these tests, there has been a tradeoff between speed of results and accuracy, and the untrained can have difficulty interpreting results. That tradeoff is important in deciding when and how to deploy rapid tests. However, it is also becoming less of an issue as technologies, such as CRISPR-based diagnostics, come available and as many improve to increase sensitivity in point-of-person tests.<sup>26</sup>

CRISPR-based diagnostics have the potential to attain the accuracy of a PCR test with the rapidity of a rapid test. More generally, CRISPR-based tests could have:

- High accuracy,<sup>27</sup>
- Quick results,<sup>28</sup>
- Low cost and complexity, and <sup>29</sup>
- Rapid reconfiguration to test for a new pathogen<sup>30</sup>

<sup>25</sup> Giorgia Guglielmi, “[Rapid Coronavirus Tests: A Guide for the Perplexed](#),” *Nature News Feature*, February 9, 2021.

<sup>26</sup> James P. Broughton, Xianding Deng, Guixia Yu, Clare L. Fasching, Venice Servellita, Jasmeet Singh, Xin Miao, et al., “[CRISPR–Cas12-based detection of SARS-CoV-2](#),” *Nature Biotechnology* 38, no. 7 (2020): 870-874; Renee Shenton, “[A Sense for What is Important](#),” Breakout Ventures, October 20, 2020.

<sup>27</sup> Uyanga Ganbaatar and Changchun Liu, “[CRISPR-Based COVID-19 Testing: Toward Next-Generation Point-of-Care Diagnostics](#),” *Frontiers in Cellular and Infection Microbiology* 11 (2021).

<sup>28</sup> Ibid.

<sup>29</sup> Amy Maxmen, “[Faster, Better, Cheaper: The Rise of Crispr in Disease Detection](#),” *Nature* 566, no. 7745 (2019): 437-438.

<sup>30</sup> Uyanga Ganbaatar and Changchun Liu, “[CRISPR-Based COVID-19 Testing: Toward Next-Generation Point-of-Care Diagnostics](#),” *Frontiers in Cellular and Infection Microbiology* 11 (2021).

CRISPR-based tests and similar ones should be deployed immediately after detection of an infectious disease outbreak to help better understand and characterize how quickly the pathogen is spreading and, correspondingly, aid in confirming rates of hospitalization or death.

The international community will also need to develop and maintain sufficient infrastructure, including manufacturing capacity and logistical chains, to be ready for when outbreaks require rapid, cheap, highly accurate tests to identify those who are infected, limit their spreading pathogens as much as possible, and support contact tracing. An especially interesting use case is to deploy these rapid tests at border crossings for use during a known outbreak to better isolate it within the country of origin.

Point-of-person tests should also be a fundamental part of biosafety in labs, reducing the risk that a lab accident will turn into a global pandemic. If a laboratory worker handling a dangerous biological agent is suspected of being sick, these tests should be used to check whether an accident may have occurred.

### **Next Steps**

#### **Ready for Procurement and/or Scaling**

- Use existing, non-CRISPR-based pathogen-specific tests in BSL-3 and 4 laboratories, with a focus on selecting tests that are rapid and accurate.

#### **Advanced Development, Testing and Evaluation**

- Create innovative means of sample acquisition.
- Develop rapid, highly accurate, paper-based tests that can be reconfigured quickly and manufactured at scale in case of an outbreak or to aid in tracking/controlling high-priority endemic disease.
- Plan for surge capacity to rapidly create pathogen-specific diagnostic tests.
- Pilot projects to use CRISPR-based, pathogen specific detection for tracking/controlling high priority endemic diseases.
- Pilot projects to use diagnostics targeted at pathogens in labs as a biosafety precaution, to be applied in combination with wearables, which would be the first line of defense.
- Develop novel methods of using rapid diagnostic tests, e.g., a traveller takes a test when they enter an airport and it provides the results as they pass through security.
- Combine rapid diagnostic tests with automated means of interpreting those same tests so that users can more easily take into account issues around accuracy (sensitivity/specificity).

#### **Early-Stage Research through Advanced Technology Development**

- Develop processes for rapidly distributing tests to large portions of a population, in addition to developing tests that can be sent through the mail.
- Research new methods of sample acquisition that are non-invasive and targeted at other types of samples, e.g., blood instead of saliva or mucus.
- Research into rapid molecular tests (such as CRISPR) that do not require amplification of genetic material.

#### **High-Risk, High-Payoff Research (i.e., Moonshots)**

- Develop tests that are so rapid that they can be used for entry into buildings or hospitals, or used in airports or at borders. The goal would be to have tests that provide highly-accurate results in seconds.
- Integrate rapid tests into clothing such as masks.

### *Digital Detection*

Pathogens can spread exponentially. Early in the SARS-CoV-2 pandemic, for each new case, an additional two to four cases resulted on average. The real-time sharing of data that may indicate outbreaks makes it a key component of early warning. There are organizations that are applying approaches like artificial intelligence/machine learning as effective early warning tools. The company BlueDot was one of the first organizations to sound an alarm internationally about the SARS-CoV-2 outbreak.<sup>31</sup> BlueDot scours the internet and obtains, integrates, and analyzes various official and unofficial datasets for signs of an impending pathogen outbreak. BlueDot and organizations like it approached the speed of early detection of ProMED, an e-mail service that has consistently been the first to notify the world of major outbreaks such as SARS, MERS, Ebola, and the growing spread of Zika.<sup>32</sup> ProMED has a similar approach in that it looks for news, government actions, and announcements throughout the world but relies on a voluntary network of professional and amateur epidemiologists to gather, disseminate, and analyze that information.<sup>33</sup>

Today, BlueDot’s methods are most useful in notifying the world of an outbreak and placing pressure on local authorities to act (when reporting is made public). They can also serve as a trigger for other countries outside of where the outbreak is occurring to take actions like developing and deploying rapid, scalable diagnostics. Today, integrating a variety of datasets from internet searches, to social media posts, to flight information has high potential to spot outbreaks relatively early in their spread and predict where they will go.<sup>34</sup>

As a next step, organizations doing digital detection should seek to integrate more sources of information. Such organizations should also develop means of automatically generating reports to speed delivery of information to decision makers. These reports should include forecasts as to where the pathogen is likely to spread. ProMED is a useful benchmark for comparison and tracking progress in speed of detection and automated reporting for policymakers.<sup>35</sup> With more and more outbreak-relevant data streams available, there is an opportunity to further leverage this technology by integrating a wider variety of information than used today, including data from metagenomic sequencing, massively multiplexed detection data, and environmental detection system data. This should be the aim of real-time digital reporting systems that the U.S.

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<sup>31</sup> Will Douglas Heaven, “[AI Could Help with the Next Pandemic—But Not with This One](#),” *MIT Technology Review*, March 12, 2020.

<sup>32</sup> Malwina Carrion and Lawrence C. Madoff, “[PROMED-mail: 22 Years Of Digital Surveillance of Emerging Infectious Diseases](#),” *International Health* 9, no. 3 (2017): 177-183.

<sup>33</sup> *Ibid.*

<sup>34</sup> *Ibid.*

<sup>35</sup> Victor L. Yu and Lawrence C. Madoff, “[ProMED-mail: An Early Warning System for Emerging Diseases](#),” *Clinical Infectious Diseases* 39, no. 2 (2004): 227-232.

government is considering funding and organizations like the Rockefeller Foundation are championing.<sup>36</sup>

## Next Steps

### Ready for Procurement and/or Scaling

- Governments, intergovernmental bodies, and news agencies should expand partnerships with organizations today that are using machine-learning/data-based prediction of outbreaks.
- Expand coverage of open-source methods of early warning, e.g., website trawling, monitoring social media and search terms, to everywhere in the world, especially low-resource settings.
- Invest more in related IT infrastructure, including digitization of public health records, that will allow easier access to public health information in low-resource countries.
- Deploy privacy-preserving machine learning approaches to assuage privacy concerns about public health data.
- Increase access to public-health-relevant, anonymized data that is currently siloed, e.g., movements of mobile phones.

### Advanced Development, Testing and Evaluation

- Create automated, high quality reporting of incoming outbreak information to inform policymakers, including recommended actions to be taken.

### Early-Stage Research through Advanced Technology Development

- Integrate signals from health sensors such as smart thermometers and other smart devices such as smart speakers.

## CONCLUSION

The technologies outlined above and others will have to come together in order to create a global early warning system for novel biological threats. They can help create a layered approach that will help rapidly detect and track the full spectrum of biological threats.

CSR describes the main organizations and actors in pathogen early warning in its companion report, *Toward a Global Pathogen Early Warning System: Building on the Landscape of Biosurveillance Today*.<sup>37</sup> As the technologies to create a layered detection system come online, many of these organizations will be doing implementation, which will require integration with existing systems and phasing out outdated systems and efforts as time passes.

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<sup>36</sup>“[Getting Ahead of the Pandemic: Accelerating National Genomic Surveillance](#),” Report, The Rockefeller Foundation, accessed July 26, 2021; Dylan B. George, Wendy Taylor, Jeffrey Shaman, Caitlin Rivers, Brooke Paul, Tara O’Toole, Michael A. Johansson, et al., “[Technology to Advance Infectious Disease Forecasting for Outbreak Management](#),” *Nature Communications* 10, no. 1 (2019): 1-4.

<sup>37</sup> “[Toward a Global Pathogen Early Warning System: Building on the Landscape of Biosurveillance Today](#),” A product of the Janne E. Nolan Center on Strategic Weapons, an institute of the Council on Strategic Risks. Authors: Natasha Bajema, Bill Beaver, Christine Parthemore, Adejare Atanda, Joanne Horn, David Manheim, Daniel Regan, Sid Sharma, Jacob Swett, and Nikki Teran. Edited by Christine Parthemore and Francesco Femia. July 2021.

The Council on Strategic Risks is part of a community of organizations that are thinking deeply about pathogen early warning systems. Recent reports from the Milken Institute and the Rockefeller Foundation also reflect a growing consensus that pathogen early warning systems will come in diverse forms and are tailored to specific use cases to create a layered and effective system. With further development and deployment of the technologies described in this briefer, these systems can become a reality, resulting in a heightened potential to prevent future pandemics.