REPURPOSING THERAPEUTIC DRUGS FOR COVID–19: RESEARCH CHALLENGES AND OPPORTUNITIES

HEARING

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

OF THE

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTEENTH CONGRESS

SECOND SESSION

JUNE 19, 2020

Serial No. 116–74

Printed for the use of the Committee on Science, Space, and Technology

Available via the World Wide Web: http://science.house.gov

U.S. GOVERNMENT PUBLISHING OFFICE
40–634PDF WASHINGTON : 2021

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C O N T E N T S

June 19, 2020

REPURPOSING THERAPEUTIC DRUGS FOR COVID–19: RESEARCH CHALLENGES AND OPPORTUNITIES

FRIDAY, JUNE 19, 2020

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,
Washington, D.C.

The Subcommittee met, pursuant to notice, at 1:30 p.m., via Webex, Hon. Bill Foster [Chairman of the Subcommittee] presiding.

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES
SUBCOMMITTEE ON INVESTIGATIONS & OVERSIGHT

HEARING CHARTER

Repurposing Therapeutic Drugs for COVID-19: Research Challenges and Opportunities

Friday, June 19, 2020
1:30 p.m. ET
Cisco WebEx

PURPOSE

The purpose of the hearing is to explore the scientific foundations behind repurposing existing drugs for the treatment of COVID-19. The Subcommittee will discuss how researchers identify and test approved drugs—developed for other uses—that could lessen the severity of COVID-19 symptoms and the regulatory approval process for the use of these drugs among infected patients. The Subcommittee will also explore how the Federal government conducts oversight and supports research in this area and how these processes have been affected by the current pandemic.

WITNESSES

- **Dr. Peter Lurie**, President, Center for Science in the Public Interest
- **Dr. James Finigan**, Director of the Respiratory Centers of Excellence, National Jewish Health
- **Dr. Rick Stevens**, Associate Laboratory Director for Computing, Environment and Life Sciences, Argonne National Laboratory
- **Dr. Benjamin Rome**, Associate Physician, Brigham and Women's Hospital; Postdoctoral Research Fellow, Harvard Medical School

KEY QUESTIONS

- How can existing FDA-approved drugs be used to treat COVID-19?
- How does the approval process for repurposed therapeutics differ from the traditional drug approval process?
- How should existing research and approval mechanisms be altered to meet the urgent need created by the ongoing pandemic?
- How can the Federal government support research into repurposing existing drugs that might not be profitable for industry?
- How have the Emergency Use Authorizations issued over the course of the pandemic adhered to best practices and the principles of scientific integrity?
- What are the challenges of conducting clinical trials during a pandemic?
- How can the Federal government incorporate clinical trial research into its broader pandemic planning and preparedness efforts?
- What opportunities exist for conducting low-cost outpatient trials of repurposed drugs that patients could take immediately after testing positive but prior to developing symptoms?

Background

There is no single drug or treatment plan that is reliably effective in combatting COVID-19.[1] There are many research efforts attempting to address this need, including the development of new drugs and CRISPR-based therapeutics, the use of convalescent plasma, and the repurposing of drugs that have been previously approved by the Food and Drug Administration (FDA) to treat other diseases. This hearing will primarily focus on the potential to repurpose drugs that have been deemed safe and effective for other diseases.

More than 2,000 studies addressing various aspects of COVID-19 are registered on ClinicalTrials.gov, including almost 50 federally funded clinical studies.[2] Many of these trials are directed at treatment, and the results of numerous trials involving therapies will be reported over the next few weeks and months.[3] It is vitally important that these study results are interpreted and presented clearly, and appropriately communicated to clinicians, the public, and policymakers.

Conducting Clinical Trials for COVID-19 Therapeutics

Large randomized, placebo-controlled trials are the ideal way to determine whether a drug is safe and effective at treating COVID-19. These are prospective studies that reduce bias and provide a rigorous tool to examine cause-effect relationships between an intervention and a health outcome.[4] Unfortunately, these types of trials are expensive, and private industry tends to fund clinical trials that promise to reap financial rewards. Shrinking Federal funding has made industry an important source of research; however, companies with financial interests in studies have more control over what doctors and patients learn about new treatments.[5]

During COVID-19, it seems that numerous, small stand-alone trials and observational studies of single treatments or interventions have grown, in part due to uncoordinated clinical research.[6] Some fear that so many trials have launched in response to COVID-19 that this could actually prevent studies from producing useful results — either because some may be potentially redundant or because each study does not involve enough patients to reach accurate conclusions.[7]

Clinical trials are much more difficult to conduct during pandemics. Researchers, institutional review boards, and regulators are accustomed to developing trial plans over months, not weeks.[8] Healthcare workers and trial coordinators must collect detailed data at regular intervals; this is

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[1] "Treatments for COVID-19," Harvard Health Publishing, Updated June 5, 2020, accessed here: https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19

[2] See https://clinicaltrials.gov/ct2/results/details?cond=COVID-19.

[3] Howard Bauchner and Phil Fontanarosa, "Randomized Clinical Trials and COVID-19: Managing Expectations," *JAMA*, May 4, 2020, accessed here: https://jamanetwork.com/journals/jama/fullarticle/2765696.

4 Eduardo Hariton and Joseph J. Locascio, "Randomized controlled trials—the gold standard for effectiveness research: Study design: randomized control trials," *BJOG*, Vol. 125(13):1716, DOI: 10.1111/1471-0528.15199, December 2018, accessed here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6235704/.

[5] Meredith Cohn, "Industry funds six times more clinical trials than feds, research shows," *Baltimore Sun*, December 15, 2015, accessed here: https://www.baltimoresun.com/health/bs-hs-trial-funding-20151214-story.html.

[6] Hans-Georg Eichler, et al, "Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?" *Clinical Pharmacology & Therapeutics*, DOI: https://doi.org/10.1002/cpt.1891, May 14, 2020, accessed here: https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1891.

[7] Zachary Brennan, "The latest obstacle in the search for a coronavirus treatment: Too many drug trials," *Politico*, April 30, 2020, accessed here: https://www.politico.com/news/2020/04/30/coronavirus-drug-treatment-trials-227508.

[8] R. Kiplin Guy, et al, "Rapid repurposing of drugs for COVID-19," *Science*, Vol. 368, Issue 6493, pp.829-830, DOI: 10.1126/science.abb9332, May 22, 2020, accessed here: https://science.sciencemag.org/content/368/6493/829.

harder when they lack adequate personal protective equipment and their workloads are already stretched thin.

Recruiting patients can also be challenging; even under ideal settings, trials can fail due to a lack of patient enrollment. An early explosion of cases followed by a steady decrease means that the recruitment window remains open only for a small amount of time. During the 2014-2016 Ebola outbreak in West Africa, for instance, the National Institutes of Health (NIH) was forced to cancel a trial of a promising therapeutic after the outbreak's decline made it impossible to find enough participants.[9]

In addition, physicians at trial sites that evaluated Gilead's remdesivir in Boston, New York, and Atlanta faced barriers to recruiting minority patients in clinical trials. Some of the sites working on the NIH-funded trial said that they did not receive consent forms for the study in Spanish.[10] To avoid wasting personal protective equipment, physicians working with translators had to call into the COVID-19 patients' rooms instead of being at the bedside. Some of the researchers said that explaining the study and getting consent took up to four hours, per patient.[11]

Researchers argue that *"for every week that trials do not deliver, more and more patients are exposed to the wrong treatments, which well-designed and rapidly run clinical trials could have taken off the table, making space to pursue, other, and ultimately more meaningful, therapeutic options."*[12] Without coordinated clinical research, well-funded scientific infrastructure, and reasonable regulatory flexibility and oversight, our efforts to find treatments for COVID-19 will be delayed.

Larger "platform" trials, like the World Health Organization's Solidarity clinical trial, facilitate the comparison of multiple treatments and approaches within a trial and across trials.[13] The FDA could encourage researchers to leverage "master protocols" that allow them to test multiple potential COVID-19 therapies at once.[14] However, the FDA does not have the power to coordinate trials—only to approve their design based on safety and efficacy criteria.[15]

FDA Approval for Repurposed Therapeutics

Developing COVID-19 therapeutics by repurposing approved drugs used for other illnesses takes advantage of existing information to enable rapid clinical trials and regulatory review.[16] Researchers can screen numerous drugs at one time, testing whether they may have an

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[9] During a subsequent Ebola outbreak in 2019, the NIH was able to generate enough clinical evidence to show that the therapeutic was ineffective. Zachary Brennan, "The latest obstacle in the search for a coronavirus treatment: Too many drug trials," *Politico*, April 30, 2020, accessed here: https://www.politico.com/news/2020/04/30/coronavirus-drug-treatment-trials-227508.

[10] Zachary Brennan, "Hit hard by the coronavirus, minorities find access to potential COVID-19 drugs via hospitalizations," *Politico*, May 20, 2020.

[11] *Id.*

[12] Hans-Georg Eichler, et al, "Clinical Trials for COVID-19: Can we Better Use the Short Window of Opportunity?" *Clinical Pharmacology & Therapeutics*, DOI: https://doi.org/10.1002/cpt.1891, May 14, 2020, accessed here: https://ascpt.onlinelibrary.wiley.com/doi/full/10.1002/cpt.1891.

[13] *Id.*

[14] Stephen Hahn, Peter Marks, and Janet Woodcock, "The Path Forward: Coronavirus Treatment Acceleration Program," FDA, April 20, 2020, accessed here: https://www.fda.gov/news-events/fda-voices/path-forward-coronavirus-treatment-acceleration-program.

[15] Zachary Brennan, "The latest obstacle in the search for a coronavirus treatment: Too many drug trials," *Politico*, April 30, 2020, accessed here: https://www.politico.com/news/2020/04/30/coronavirus-drug-treatment-trials-227508.

[16] R. Kiplin Guy, et al, "Rapid repurposing of drugs for COVID-19," *Science*, Vol. 368, Issue 6493, pp.829-830, DOI: 10.1126/science.abb9332, May 22, 2020, accessed here: https://science.sciencemag.org/content/368/6493/829.

unexpected potential to fight the SARS-CoV-2 virus, and then narrow down a list of the most promising candidates.[17] Preclinical testing can move faster since scientists already have a general understanding of these drugs' toxicity, efficacy, and safety information.

When the FDA approves a drug for a particular purpose, it allows the company selling the drug to label and market it for that purpose. These approvals are made after the company submits sufficient evidence that the drug is safe and effective. *In vitro*, or "test tube" tests, and animal studies provide mechanistic information, giving preliminary evidence that the drug has the intended effect on the virus being studied. Companies then use this information to apply for FDA approval to move into clinical trials. These consist of three phases of testing, where controlled experiments are done on increasingly larger populations to determine the safety and efficacy of the drug.[18] The FDA's Center for Drug Evaluation and Research (CDER) then reviews the information submitted by pharmaceutical companies and determines whether the demonstrated benefits of the drug outweigh any demonstrated risks.

When a drug is finally granted FDA approval, a company has received permission to market it for the specific indications that were tested and reviewed by the FDA. However, physicians are legally permitted to prescribe drugs for off-label purposes that have not been studied by the company or approved by FDA.[19] In order for an approved drug to be labeled and marketed for another purpose, the same clinical trial process must occur. Safety trials can typically be expedited, due to the drug's prior clinical trials, but key questions must still be answered. The population taking the drug for its labelled use might be entirely different than the population that would take it for COVID-19 treatment. For example, there exists a wealth of information in the FDA's safety database on the benefits and risks of taking hydroxychloroquine for lupus or arthritis. However, patients sick with COVID-19 may be older and sicker, and the disease may have compromised organs that tend to be healthy in the typical lupus or arthritis patient. Thus, CDER's risk-benefit calculation – the determining factor for FDA approval – is fundamentally different when the drug is applied to a different disease in a different population. For example, a higher level of risk might be acceptable for a deadlier disease; or, if a drug is less effective on COVID-19 than it is for its approved use, its toxicity levels may be deemed unacceptable given the only marginal benefit.

Numerous drugs are currently being tested for their effectiveness against COVID-19. Most notable are hydroxychloroquine and chloroquine, which have been FDA-approved as anti-malarials[20] and have scientific support for several off-label uses; remdesivir, an antiviral that currently has no FDA-approved uses;[21] and famotidine, an over-the-counter heartburn

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[17] Carl Zimmer, "Old Drugs May Find a New Purpose: Fighting the Coronavirus," *New York Times*, May 1, 2020, accessed here: https://www.nytimes.com/2020/04/30/health/coronavirus-antiviral-drugs.html.
[18] "Development and Approval Process | Drugs," U.S. Food and Drug Administration, accessed here: https://www.fda.gov/drugs/development-approval-process-drugs
[19] Rebecca Dresser and Joel Frader, "Off-Label Prescribing: A Call for Heightened Professional and Government Oversight," The Journal of Law, Medicine, and Ethics, Fall 2009, accessed here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2836889/
[20] "Plaquenil," U.S. Food and Drug Administration, accessed here: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf
[21] Andrew Joseph, "As the coronavirus spreads, a drug that once raised the world's hopes is given a second shot," Stat News, March 16, 2020, accessed here: https://www.statnews.com/2020/03/16/remdesivir-surges-ahead-against-coronavirus/

medication.[22] Remdesivir has been granted an Emergency Use Authorization (EUA) for the treatment of COVID-19, based on preliminary clinical trial results.[23]

Emergency Use Authorizations

The Secretary of Health and Human Services (HHS) has the authority to grant EUAs to facilitate the availability of medical products during public health emergencies. This allows the Federal government to provide state and local governments with medical supplies through the Strategic National Stockpile. HHS can grant EUAs to unapproved drugs, or to off-label uses for drugs. A public health emergency must be declared in order for HHS to issue EUAs, and the EUA elapses once the public health crisis has concluded.[24]

The standards for granting an EUA are much lower than the standards for FDA approval of a drug. The FDA may issue an EUA if "it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition."[25] There are no public hearings held to solicit comment as there would be in a drug approval process, and only a few senior FDA officials might review the EUA, rather than a number of FDA staff and scientists.[26]

Hydroxychloroquine

On March 28, the FDA issued an EUA for hydroxychloroquine and chloroquine, anti-malarial medications that have been approved for use in lupus and arthritis cases. Chloroquine has shown anti-viral properties in various *in vitro* tests, and it has been proposed as a treatment for numerous diseases, including SARS, Ebola, dengue, Zika, and chikungunya. However, in animal studies, chloroquine was not effective in combatting these viruses, and in some cases exacerbated the diseases.[27] Hydroxychloroquine and chloroquine entered the COVID-19 conversation in March, when various media outlets began reporting on the drugs' potential antiviral properties, and a French paper was published suggesting that a combination of hydroxychloroquine and an antibiotic had been effective in a small number of COVID-19 patients. President Trump then began publicly advocating for use of the drugs on his Twitter account and at White House press briefings.[28] On March 23, he announced, "At my direction, the

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[22] Elizabeth Cohen, "Common heartburn drug may have helped 10 patients at home with Covid-19," *CNN*, June 5, 2020, accessed here: https://www.cnn.com/2020/06/04/health/famotidine-covid-19-case-series-study/index.html

[23] "Emergency Use Authorization," U.S. Food and Drug Administration, Updated June 13, 2020, accessed here: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs

[24] "FAQs on Emergency Use Authorizations (EUAs) for Medical Devices During the COVID-19 Pandemic," U.S. Food and Drug Administration, April 29, 2020, accessed here: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-emergency-use-authorizations-euas-medical-devices-during-covid-19-pandemic

[25] "Emergency Use Authorization," U.S. Food and Drug Administration | Public Health Emergency, September 5, 2019, accessed here: https://www.phe.gov/Preparedness/planning/authority/Pages/eua.aspx

[26] Nicholas Florko, "Why was an obscure federal bureaucrat involved in Trump's emergency hydroxychloroquine authorization?," *Stat News*, April 24, 2020, accessed here: https://www.statnews.com/2020/04/24/why-rick-bright-involved-hydroxychloroquine/

[27] Franck Tournet and Xavier de Lamballerie, "Of chloroquine and COVID-19," *Antiviral Research*, Vol. 177, May 2020, accessed here: https://www.sciencedirect.com/science/article/pii/S0166354220301145?via%3Dihub

[28] Philip Bump, "The rise and fall of Trump's obsession with hydroxychloroquine," *Washington Post*, April 24, 2020, accessed here: https://www.washingtonpost.com/politics/2020/04/24/rise-fall-trumps-obsession-with-hydroxychloroquine/

federal government is working to help obtain large quantities of chloroquine."[29] The FDA issued an EUA for chloroquine and hydroxychloroquine on March 28.[30]

The decision to issue an EUA came under fire from scientists, including a number of former FDA officials. While FDA has the flexibility to extend EUAs to drugs that do not meet the threshold for FDA approval – and while this flexibility is important – experts were concerned that the lack of any clinical evidence for hydroxychloroquine's and chloroquine's effectiveness would send a confusing, and potentially harmful, message. Furthermore, widespread use of the drugs would potentially interfere with researchers' ability to collect meaningful data.[31]

On June 15, the FDA revoked the EUA for hydroxychloroquine and chloroquine after concluding that it is "no longer reasonable to believe that oral formulations of [hydroxychloroquine] and [chloroquine] may be effective in treating COVID-19, nor is it reasonable to believe that the known and potential benefits of these products outweigh their known and potential risks."[32] The notice of revocation noted that previous findings regarding the drugs' effect on viral shedding have not been replicated in controlled experiments, and that no experiments have shown decreased mortality or other positive outcomes due to use of the drugs.[33]

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[29] *Id.*
[30] Letter from Denise M. Hinton to Rick Bright, "Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease," U.S. Food and Drug Administration, March 28, 2020, accessed here: https://www.fda.gov/media/136534/download
[31] Charles Piller, "Former FDA leaders decry emergency authorization of malaria drugs for coronavirus," *Science*, April 7, 2020, accessed here: https://www.sciencemag.org/news/2020/04/former-fda-leaders-decry-emergency-authorization-malaria-drugs-coronavirus
[32] Letter from Denise M. Hinton to Gary L. Disbrow, U.S. Food and Drug Administration, June 15, 2020, accessed here: https://www.fda.gov/media/138945/download
[33] *Id.*

Chairman FOSTER. Without objection, the Chair is authorized to declare recess at any time.

Before I deliver my opening remarks, I wanted to note the unusual circumstances under which we're meeting today. Pursuant to Resolution 965, today, the Subcommittee will be meeting virtually. This is not how any of us would prefer to perform our duties, but remote work is unfortunately a necessity at the current moment and a reflection of the part we all have to play in slowing the spread of COVID–19.

In light of this remote format, I want to offer some reminders to the Members about the conduct of the hearing. Members should keep their video feed on as long as they are present at the hearing. Members are responsible for muting and unmuting their own microphones, and please keep your microphones muted unless you're speaking. You know, much as we love your family dog [audio malfunction].

And finally, if Members have documents they wish to submit for the record, please email them to the Committee Clerk, whose email address was circulated prior to the hearing.

Well, good afternoon and welcome to the first virtual hearing of the Committee on Investigations and Oversight. Today, we're discussing a critical issue: research into repurposing of existing therapeutic drugs for COVID–19 treatment, as well as the scientific basis for the Federal Government's evaluation of such drugs.

I appreciate our witnesses being here under these unusual circumstances, but these are very important issues, and we look forward to your testimony.

Today's hearing revolves around one of humanity's most promising tools in its public health response to the current pandemic: repurposing existing therapeutic drugs to treat COVID–19. The appeal of repurposing existing therapeutics is obvious. These drugs have already been developed, they have already been manufactured, and in some cases can quickly be accessed in large quantities. And for drugs that have already been approved to treat other diseases, a certain amount of safety data is often available to regulators.

In the absence of any COVID–19 vaccine or novel treatment, existing therapeutics could potentially offer critical assistance for severely ill patients and bridge the gap until more prevention and treatment options become available. But with great promise comes great concerns. Since existing therapeutics rest at our fingertips and have demonstrated benefits in other circumstances, it can be all too easy in the midst of a pandemic to cut corners and to seek shortcuts to longstanding regulatory processes, and we can't allow that to happen. The evaluation process to repurpose approved drugs is there for a reason: to ensure that existing therapeutics, which could carry significant health risks for COVID–19 patients, are assessed through the prism of scientific and medical data and sanctioned on the basis of factual evidence regarding safety and efficacy in their new context. And while the process itself should be flexible and as fast as possible, the integrity of the process must be firmly upheld.

The research community's evidence-based evaluation of existing therapeutics must be paramount, and political considerations must

never enter into the equation for any specific treatment. If politics is allowed to interfere, scientific research may be distorted, patients may be placed at risk, and the faith of the public in our whole public health mechanism may be shaken.

Unfortunately, we're seeing the consequences of some political interference in the controversy surrounding two existing therapeutic drugs, chloroquine and hydroxychloroquine. In March, the FDA (Food and Drug Administration) issued an emergency use authorization (EUA) for these drugs as COVID–19 treatments. The scientific evidence to support this decision was dangerously thin, but the political considerations were clear. And our President became the world's loudest cheerleader for both drugs. Researchers, experts, and former FDA officials all questioned the decision for lacking a sufficient scientific basis.

And now, nearly 3 months later, the FDA just this week revoked the emergency use authorization, acknowledging the clinical data showing the drugs, quote, "may not be effective to treat COVID–19" and that, quote, the "potential benefits for such use do not outweigh the known and potential risks." This is a clear example of the dangers of allowing political considerations to distort what should be a scientific process reliant upon unbiased scientific evaluation.

This hearing will explore the importance of supporting scientific research into repurposing existing therapeutics as COVID–19 treatments and the cost of neglecting science when politics intrudes. The research community is currently engaged in a heroic effort to explore as many therapeutics as possible in the search for a COVID treatment. The Federal Government supports many of these efforts, but there may be more that we can do as policymakers to provide researchers with the funding and the conditions that they need to make progress. And there may also be more that we can do to uphold the integrity in the role of science as the foundation for Federal efforts in this area.

Our witnesses bring diverse perspectives with deep experience in these areas. I look forward to learning from them about the most effective way for the Federal Government to support research into repurposing existing therapeutics for this pandemic and probably—unfortunately, probably for the next one. Well, thank you all.

[The prepared statement of Chairman Foster follows:]

Today's hearing revolves around one of humanity's most promising tools in its public health response to the current pandemic: repurposing existing therapeutic drugs to treat COVID-19. The appeal of repurposing existing therapeutics is obvious. These drugs have already been developed; they have already been manufactured, and in many cases can quickly be accessed in large quantities; and for drugs that have already been approved to treat other diseases, a certain amount of safety data is already available to regulators. In the absence of any COVID-19 vaccine or novel treatment, existing therapeutics could potentially offer critical assistance for severely ill patients and bridge the gap until more prevention and treatment options become available.

But with great promise comes great temptation. Since existing therapeutics rest at our fingertips and have demonstrated benefits in other circumstances, it can be all too easy in the midst of a pandemic to cut corners and seek shortcuts to longstanding regulatory processes. We cannot allow this to happen. The evaluation process to repurpose approved drugs exists for a reason: to ensure that existing therapeutics, which could carry significant health risks for COVID-19 patients, are assessed through the prism of scientific and medical data and sanctioned on the basis of factual evidence regarding safety and efficacy in their new context. While the

process itself should be flexible, the integrity of the process must be firmly upheld. The research community's evidence-based evaluation of existing therapeutics must be paramount, and political considerations must never enter into the equation for any specific treatment. If politics is allowed to interfere, scientific research may be distorted, patients may be placed at risk, and the faith of the public may be shaken.

Unfortunately, we are seeing the consequences of political interference in the controversy surrounding two existing therapeutic drugs, chloroquine and hydroxychloroquine. In March, the FDA issued an Emergency Use Authorization for the drugs as COVID-19 treatments. The scientific evidence to support this decision was dangerously thin, but the political considerations were clear: President Trump had become the world's loudest cheerleader for both drugs. Researchers, experts, and former FDA officials all criticized the decision for lacking a sufficient scientific basis. Now, nearly three months later, the FDA just this week revoked the EUA, acknowledging clinical data showing that the drugs "may not be effective to treat COVID-19" and that the "potential benefits for such use do not outweigh its known and potential risks." This is a clear example of the dangers of allowing political considerations to distort a process reliant upon unbiased scientific evaluation.

This hearing will explore the importance of supporting scientific research into repurposing existing therapeutics as COVID-19 treatments, and the costs of neglecting science when politics intrudes. The research community is currently engaged in a heroic effort to explore as many existing therapeutics as possible in the search for a COVID treatment. The federal government supports some of these efforts, but there may be more we can do as policymakers to provide researchers with the funding and the conditions they need to make progress. There may also be more we can do to uphold the integrity of the role of science as the foundation for federal efforts in this area. Our witnesses bring diverse perspectives with deep experience on these issues. I look forward to learning from them about the most effective way for the federal government to support research into repurposing existing therapeutics, now and for the next pandemic.

Chairman FOSTER. And the Chair will now recognize Mr. Lucas, the Chair of the Full Committee, for an opening statement.

Mr. LUCAS. Thank you, Chairman Foster, and thank you to our witnesses for their participation today.

The COVID–19 pandemic is unlike anything we've faced since the 1918 Spanish flu. In those days, we had very few tools to slow the spread of the virus, develop treatments, or produce a vaccine to make ourselves immune to it. Thankfully, that has changed. Our Nation's research enterprise, including government, academia, and industry, is the expertise, resources, and talent needed to fight this pandemic. The work they're doing to model the virus, screen potential treatments, and engineer new medical equipment is truly lifesaving.

We have supercomputers, advanced manufacturing techniques, and even advanced photon sources being used to fight COVID–19. From PPE (personal protective equipment) manufacturing and new vaccine developments to repurpose existing therapeutics, America's scientific community has heeded the call to action.

An excellent example of the public-private collaboration, leveraging technology to fight a common cause, is the COVID–19 High-Performance Computing Consortium. Though this OSTP (Office of Science and Technology Policy)-led collaboration, COVID–19 researchers can access the world's most powerful computing resources to run complex models and develop large numbers of calculations at astonishing speeds. By leveraging these computing resources and deploying artificial intelligence (AI) and machine-learning techniques, researchers can determine which drugs have the potential to be repurposed against COVID–19 at a speed and scale previously unthinkable. Technology will continue to play a critical role in saving lives and preventing the spread of COVID–

19. And our Federal research enterprise must have access to the resources and the technology necessary to do their jobs and to do it well.

That's why I introduced the *"COVID Research Act of 2020"*, which would create an interagency working group and establish a national strategy to address infectious diseases. Additionally, this bill authorizes $50 million for DOE's (Department of Energy's) infectious disease research program over the next two years. Working together with NASA (National Aeronautics and Space Administration) and the NSF (National Science Foundation), this program gives us the ability to utilize the Federal Government's computing resources to respond to infectious diseases.

Our national labs have already demonstrated the value of using high-performance computing and advanced research facilities to model novel coronavirus, understand its effects on human cells, and predict its spread. I'm pleased to learn that there is work underway at Argonne National Lab that is particularly relevant to repurposing therapeutics to fight COVID–19.

And thank you, Dr. Stevens, for being here today. I look forward to learning more about this important work.

And, more broadly, I'd like to extend my thanks to the entire scientific community, researcher after researcher, lab after lab pivoting immediately to fight COVID–19 when it reached our shores.

When I began serving as Ranking Member of the Committee, I said one of our most important responsibilities is to tell the story of science and to make sure our constituents understand the tremendous research being done and why it matters to the next generation of Americans. This story in particular, how American scientists, researchers, and engineers responded to COVID–19 is one everyone should know, and I hope my colleagues will use this hearing as one more opportunity to share this work.

And with that, Mr. Chairman, I yield back.

[The prepared statement of Mr. Lucas follows:]

Thank you, Chairman Foster. And thank you to our witnesses for your participation today.The COVID-19 pandemic is unlike anything we have faced since the 1918 Spanish flu. At the time, we had very few tools to slow the spread of the virus, develop treatments, or produce a vaccine to make ourselves immune to it. Thankfully, that has changed.

Our nation's research enterprise, including government, academia, and industry, has the expertise, resources, and talent needed to fight this pandemic. The work they're doing to model the virus, screen potential treatments, and engineer new medical equipment is truly lifesaving.

We have supercomputers, advanced manufacturing techniques, and even advanced photon sources being used to fight COVID-19. From PPE manufacturing and new vaccine development to repurposing existing therapeutics, America's scientific community has heeded the call to action.

An excellent example of public-private collaboration leveraging technology to fight a common cause is the COVID-19 High Performance Computing Consortium. Through this OSTP-led collaboration, COVID-19 researchers can access the world's most powerful computing resources to run complex models and perform large numbers of calculations at astounding speeds.

By leveraging these computing resources and employing artificial intelligence and machine learning techniques, researchers can determine which drugs have the potential to be repurposed against COVID-19, at a speed and scale previously unthinkable. Technology will continue to play a critical role in saving lives and preventing the spread of COVID-19. And our federal research enterprise must have access to the resources and technology necessary to do their jobs, and to do it well.

That's why I introduced the *COVID Research Act of 2020*, which would create an interagency working group and establish a national strategy to address infectious

diseases. Additionally, this bill authorizes $50 million for DOE's Infectious Disease Research Program over the next two years. Working together with NASA and NSF, this program gives us the ability to fully utilize the federal government's computing resources to respond to infectious diseases.

Our National Labs have already demonstrated the value of using high-performance supercomputing and advanced research facilities to model the novel coronavirus, understand its effects on human cells, and predict its spread. I'm pleased to learn that there is work underway at Argonne National Lab that is particularly relevant to repurposing therapeutics to fight COVID-19. Thank you, Dr. Stevens, for being here today. I look forward to learning more about this important work. And, more broadly, I'd like to extend my thanks to the entire scientific community. Researcher after researcher and lab after lab pivoted immediately to fight COVID-19 when it reached our shores.

When I began serving as Ranking Member of this Committee, I said that one of our most important responsibilities is to tell the story of science and make sure our constituents understand the tremendous research being done, and why it matters to the next generation of Americans.

This story in particular—how American scientists, researchers, and engineers responded to COVID-19—is one everyone should know, and I hope my colleagues will use this hearing as one more opportunity to share this work.

I yield back.

Chairman FOSTER. Thank you. And if there are Members who wish to submit additional opening statements, your statements will be added to the record at this point.

[The prepared statement of Chairwoman Johnson follows:]

Thank you, Chairman, Foster, and thank you to all of our esteemed witnesses for appearing before the Subcommittee today. It is so important to learn from experts about these critical issues because the threat of COVID-19 has not diminished. I have seen in recent days, in Dallas and throughout the state of Texas, how precarious our situation truly is and how we all must reinforce our commitment to combating the pandemic. It has been clear from the beginning and it remains clear today: science-based policymaking, rooted in facts and guided by the best efforts of the scientific community, is the key to overcoming this challenge. I am glad that today's hearing can help inform the federal government's response to the pandemic in the months to come.

Repurposing existing therapeutics for COVID-19 treatment would be an important tool in the world's pandemic toolkit. Until a vaccine emerges, we must do everything possible to develop treatments that can save lives, and it makes a great deal of sense to evaluate drugs that have already been approved in other circumstances. I have been encouraged by the immense effort and resources that America's research community has dedicated to this cause. The federal government should be doing everything in its power to promote these research efforts, and I am eager to learn how we can do more to support the research community's critical work.

I also want to better understand how the federal government can work with the research community to prepare for the next pandemic. There may be opportunities for the federal government to collaborate with the research community on broad issues such as prioritizing certain drug candidates, efficiently deploying limited resources, and coordinating efforts among the vast network of research institutions engaged in this work. These questions must be approached in a deliberative manner, and we should start to consider them now so that we are better prepared next time.

As we think about these issues, we must never lose sight of the paramount importance of upholding scientific integrity at all times. Repurposing existing drugs in the midst of a pandemic carries high stakes, and federal policymaking must be done the right way, based solely on thebest available science and free from any political interference. The controversy surrounding the FDA's Emergency Use Authorization for hydroxychloroquine demonstrates all too well the damage that can occur when political considerations inappropriately influence the process. The government's actions to address the nation's needs during this public health crisis must only be guided by scientific evidence—never political pressure.

The research community is rising to the challenge of COVID-19, and I have no doubt that it will continue to perform magnificently. Thank you again to all of the witnesses. I yield back.

Chairman FOSTER. At this point I'd like to introduce the witnesses. Our first witness is Dr. Peter Lurie. Dr. Lurie is the Presi-

dent of the Center for Science in the Public Interest (CSPI), a nonprofit health advocacy group based in Washington, DC. Before joining CSPI, he held several positions at the Food and Drug Administration, including a stint at the—as the FDA's Associate Commissioner for Public Health Strategy and Analysis. He served nearly 8 years as a top official of the FDA.

Our next witness is Dr. James Finigan. Dr. Finigan is the Director of the Respiratory Centers of Excellence at National Jewish Health, the Nation's leading respiratory hospital. He's also the Medical Director of the Lung Cancer Screening Program at the National Jewish Health. Dr. Finigan is a pulmonologist with a research focus on lung cancer and injury.

Our third witness is Dr. Rick Stevens. Dr. Stevens is the Associate Laboratory Director for Computing, Environment, and Life Sciences at Argonne National Laboratory. He also serves as the leader of Argonne's Exascale Computing initiative. He's worked at Argonne Lab since 1982.

Our final witness is Dr. Benjamin Rome. Dr. Rome is an Associate Physician at Brigham and Women's Hospital in Boston, Massachusetts. He's also a Postdoctoral Research Fellow at Harvard Medical School. Dr. Rome's academic research focuses on the FDA approval process for drugs and medical devices, as well as the effect of Federal policies and regulations on drug pricing and utilization.

As our witnesses should know, each of you have 5 minutes for your spoken testimony. Your written testimony will be included in the record for the hearing. And when you've all completed your spoken testimony, we will begin with questions. Each Member will have 5 minutes to question the panel. And if there is time, we may be able to have a second round of questions from those Members who are in attendance.

And we'll now start with Dr. Lurie.

TESTIMONY OF DR. PETER LURIE, PRESIDENT, CENTER FOR SCIENCE IN THE PUBLIC INTEREST

Dr. LURIE. Well, thank you, Chairman Foster, Ranking Member Lucas, and other Committee Members, for inviting me to testify on this important topic. For this testimony, I'm defining repurposed drugs as approved drugs for which a second indication for COVID–19 is sought. Some other witnesses may use other definitions.

Unfortunately, the unmistakable allure of repurposed drugs is not enough on its own. Effectiveness for one condition does not guarantee effectiveness for a second even closely related condition. Target populations may be demographically and medically different, and so even the existing safety databases may have only limited relevance. The product may be administered in different doses or by different routes than for the first condition.

So, let's look at two repurposed drugs. The antimalarial drugs chloroquine and hydroxychloroquine, which I'm considering together, would likely have languished well down the list of candidates for COVID–19 had they not been catapulted to prominence by President Trump's comments. On March 21st, the President described them as, quote, "one of the biggest gamechangers in the

history of medicine" and later stated that he was taking the drug himself, the ultimate celebrity endorsement.

On March 28th, under pressure from the Administration, FDA granted the drugs an emergency use authorization, EUA, but the evidence provided for this EUA was less than that provided for many previous EUAs.

Eventually, the scientific process played itself out with several observational studies that demonstrated either no benefit from the drugs or even indicated that mortality rates were higher. FDA issued a warning that the drugs cause life-threatening arrhythmias. And finally, there were two randomized controlled trials, the gold standard for scientific evidence. The first suggested that the product was ineffective in preventing infection among those exposed to the virus, and the second, that it was also ineffective in treating SARS-CoV–2 infection itself. On June 15th, FDA revoked the EUA.

What can we learn from this embarrassment? Well, first, we should adhere to accepted methods of drug discovery even in a pandemic. It is the painstaking process of conducting randomized control trials that ultimately produces definitive evidence even if it is definitive evidence of lack of effectiveness.

Second, the patients in the President's phrase did have a lot to lose. Life-threatening arrhythmias were fairly common. Even patients without COVID–19 suffered as those needing hydroxychloroquine for its FDA-approved conditions had difficulty obtaining the drug due to increased demand.

Finally, the President's announcements distorted the overall research effort for COVID–19. It is inconceivable that, left to their own devices, scientists would have designed over 150 randomized controlled trials assessing the effectiveness of these drugs. How many more promising drugs were left unstudied or understudied as researchers pivoted to address the headlines?

A second problematic repurposed drug is famotidine, an over-the-counter heartburn drug also known as Pepcid, a seemingly unlikely drug for COVID–19. One of its primary advocates is a Boston physician named Dr. Michael Callahan, who was also a consultant on the Staff of the Assistant Secretary for Preparedness and Response, ASPR, Dr. Robert Kadlec. Under Dr. Kadlec's direction, Dr. Callahan, having advocated for the drug, assisted a pharmaceutical company and a hospital to prepare an application for funding to ASPR to conduct a trial of famotidine. Shortly thereafter, Dr. Kadlec ordered a hefty $21 million contract to these entities. Senior officials were cut out of the granting process.

There are two other prominent drugs worth mentioning here. The first, remdesivir, is the only drug so far proved effective against SARS-CoV–2, but it is not a repurposed drug at least in my definition. Rather, it is an unapproved drug with known antiviral activity demonstrated to be effective in a study funded by NIH (National Institutes of Health).

The second drug, dexamethasone, is the first drug to reduce mortality in patients with COVID–19. Whether it's a repurposed drug is a matter of definition as it's long been approved but is often considered as a general treatment for severe respiratory illness based

on its anti-inflammatory activity and is not directed to SARS-CoV–2 itself.

But the benefits of these two drugs were demonstrated the old-fashioned way, through rigorous, randomized controlled trials. Interestingly, the dexamethasone results are derived from the same British study that reported the ineffectiveness of hydroxychloroquine. That trial is very large and able to test multiple candidate therapies simultaneously. In contrast, the clinical trials effort in the United States has been fragmented and poorly prioritized, resulting in many relatively small studies often testing the same drugs with some patients struggling—some studies struggling to enroll patients.

In conclusion, so far in this pandemic, effective treatments have not been identified by anecdote, by wishful thinking, by Presidential pronouncement, or by questionable contracting practices. They were identified instead by the fair, transparent, and systematic application of the very scientific principles that for decades have delivered so many safe and effective treatments. But when we departed from these principles, precious time was lost, resources were squandered, and some patients paid with their lives. Thank you.

[The prepared statement of Dr. Lurie follows:]

Testimony of Peter Lurie, MD, MPH

President, Center for Science in the Public Interest

Before the U.S. House of Representatives Committee on Science, Space, & Technology

Subcommittee on Investigations and Oversight

"Repurposing Therapeutic Drugs for COVID-19; Research Challenges and Opportunities"

June 19, 2020

I want to thank Chairman Foster, Ranking Member Norman, and other committee members for inviting me to be a witness on behalf of the Center for Science in the Public Interest (CSPI) at this important hearing. CSPI is an almost 50-year-old advocacy group that is a watchdog on food and health issues on behalf of US consumers. We have been actively involved in COVID-19 issues, including building an online hub that aggregates all international databases containing evidence on COVID-19 (https://cspinet.org/covid-19-evidence-hub) and advocating for better workplace protections, particularly for those in the meatpacking industry.

The COVID-19 epidemic has produced unparalleled amounts of scientific information and has done so more rapidly than ever in history, as thousands of researchers across the globe have turned their attention to the disease. By one estimate, perhaps 52,000 papers will have been completed by mid-June. One particular focus of research has been repurposing existing drugs to treat COVID-19. This approach has an understandable allure: Such a drug would already be produced on a large scale, the product would have been found effective by the Food and Drug Administration (FDA) or other regulatory authority for a particular use, the sponsor would have

submitted data regarding the safety of the drug, and physicians would have experience prescribing it.

Unfortunately, it's not so simple. Effectiveness for one condition does not guarantee effectiveness for a second condition, even a closely related one. The target populations may be demographically and medically different and so even the existing safety database and clinical experience may have only limited relevance. The product may need to be administered in different doses or by different routes than for the first condition. Together, these factors require that FDA conduct a unique risk-benefit assessment for the potential new use.

Sad to say, shortcuts do not come often in science. And our experience with two repurposed drugs in the COVID-19 pandemic reinforces the need to adhere to established scientific principles.

The experience with the anti-malarial drugs chloroquine and hydroxychloroquine (which I will consider as one drug for the purposes of this testimony) illustrates how data-free speculation can have disastrous consequences. The drug was frequently mentioned as a potential treatment for viral infections in the past, but, despite some promising early findings in laboratory testing, it never proved effective at preventing or treating those infections in clinical studies. It would likely have languished well down the list of candidate therapies for COVID-19 had it not suddenly been catapulted to prominence by President Trump's comments. On March 21, for example, the President described it as "one of the biggest game changers in the history

of medicine" and later stated that he was taking the drug himself□—the ultimate celebrity endorsement.

On March 28, under pressure from the administration, FDA granted the drug an Emergency Use Authorization (EUA), allowing 29 million doses to be transferred to the Strategic National Stockpile. But my former FDA colleagues Jesse Goodman and Luciana Borio, both of whom have signed off on past EUAs, have attested that the evidence provided for this EUA was below that required for many previous EUAs. (The standard for EUA issuance is that "the known and potential benefits of the product, when used to diagnose, prevent, or treat the identified disease or condition, outweigh the known and potential risks of the product.") That evidence, as described in FDA's authorization letter, was comprised only of "limited in-vitro and anecdotal clinical data in case series." In other documents, the agency suggested that it also relied upon a French observational study, which was later discredited by its own publisher.

Eventually the scientific process played itself out and the inadequacies of the product to prevent or treat COVID-19 were laid bare. There were several observational studies that variously demonstrated either no benefit for the product or even indicated that mortality rates were higher among those administered the drug as treatment. One study showed that as many as 16% of hospitalized patients prescribed hydroxychloroquine, some concurrently taking other drugs like azithromycin that can also cause arrhythmias, experienced a specific arrhythmia called QT prolongation. Within weeks of the EUA, FDA issued a warning that the product could cause these life-threatening arrhythmias and reminded doctors to only use the drug in

hospitalized settings. Finally, there were two randomized, controlled trials—the gold standard for scientific evidence. The first suggested that the product was ineffective in preventing infection among those exposed to the virus and the second, still unpublished, suggested that it was also ineffective in treating COVID-19 infection itself. On June 15, shortly after the second study was publicized, FDA revoked the EUA. "The totality of scientific evidence currently available," said the agency, "indicate a lack of benefit." At that point, its adverse event reporting database already contained 25 arrhythmia reports in which the patient had died.

What can we learn from this series of events? First, this is a warning not to stray from accepted methods of drug discovery, even in a pandemic. Anecdotes are not evidence. It is the painstaking process of conducting randomized, controlled trials that ultimately produces definitive evidence—even if it is definitive evidence of lack of effectiveness.

Second, while it is tempting to believe, as the President suggested, that infected patients had nothing to lose by taking the drug, that, tragically turned out not to be the case. Life-threatening arrhythmias, as had been predicted, were fairly common, some of them fatal. Even patients without COVID-19 suffered, as those patients needing hydroxychloroquine for its FDA-approved uses (treating lupus and rheumatoid arthritis) had difficulty obtaining the drug amid sudden shortages.

Finally, the President's announcements had a distorting effect upon the overall research effort for COVID-19. It is inconceivable that, left to their own devices, scientists would have designed

over 150 randomized, controlled trials assessing the effectiveness of this drug. How many more promising drugs were left unstudied or understudied as researchers pivoted to address the headlines?

A second repurposed drug that has raised concerns is famotidine, an over-the-counter heartburn drug also known as Pepcid, a seemingly unlikely drug for COVID-19. A physician named Michael Callahan, who was working in China during the early phases of the pandemic, came to believe, based on an informal review, that COVID-19 patients who received the drug died less frequently than those who did not receive the drug. Indeed, an observational study on which Dr. Callahan was a co-author reported a significant reduction in mortality associated with famotidine use. As noted above, such findings in observational studies need to be confirmed in randomized, controlled trials.

Dr. Callahan was also a consultant on the staff of the Health and Human Services Assistant Secretary for Preparedness and Response (ASPR) Dr. Robert Kadlec. Under Dr. Kadlec's direction, Dr. Callahan assisted a pharmaceutical company, Alchem Laboratories, and Northwell Health, a hospital system in the New York City area, to prepare an application for funding to the Biomedical Advanced Research and Development Authority (BARDA), a unit within ASPR, to conduct a randomized, controlled trial of famotidine. Shortly thereafter, Dr. Kadlec ordered BARDA to award a hefty $21 million contract to Alchem, most of which covered Northwell's costs. Senior BARDA officials were cut out of the granting process.

Time will tell whether famotidine will prove effective. But the irregular process by which the contract was granted raises real questions about whether scarce government resources are being committed to the most promising therapeutic candidates.

Two other drugs used for patients with COVID-19 add additional perspectives to this discussion of repurposed drugs. The first, remdesivir, is the only drug so far proved effective against the SARS-CoV-2 virus, but is not a repurposed drug. Rather, it was an unapproved drug with known antiviral activity (not an antimalarial or an anti-heartburn drug) that was demonstrated in a randomized, controlled trial funded by the National Institutes of Health to reduce hospital stay for COVID-19 patients. Whether the second drug, dexamethasone, is a repurposed drug is a matter of definition. It was the subject of significant recent press attention because it appears to be the first drug to reduce mortality in sicker hospitalized patients with COVID-19. (The results have not yet been published.) It has long been approved, but its effectiveness is likely based not on antiviral activity; it is often considered as a general treatment for severe respiratory illness based on its anti-inflammatory activity. What links these two drugs is that their benefits were demonstrated the old-fashioned way: through rigorous randomized, controlled trials. And this experience demonstrates that such trials are feasible and can deliver favorable results even in the urgent setting of a pandemic.

The dexamethasone results are of particular note because they are derived from the same study mentioned above (the RECOVERY Trial) that reported the ineffectiveness of hydroxychloroquine in the treatment of COVID-19. In Britain, where the study was conducted,

there has been better coordination of the COVID-19 research effort, and the resultant RECOVERY trial is very large and able to test multiple candidate therapies simultaneously and rapidly. In contrast, the research effort in the United States has been fragmented and poorly prioritized, resulting in many relatively small studies, often testing the same drugs with some studies struggling to enroll patients.

In conclusion, effective treatments are not generally identified by anecdote, wishful thinking, or questionable contracting practices; they are instead the product of the fair, transparent, and systematic application of the very scientific principles that for decades have delivered so many safe and effective treatments. But when we depart from these approaches, as occurred with both hydroxychloroquine and famotidine, precious time is lost, resources are squandered, and some patients pay with their lives.

Peter Lurie, M.D., M.P.H. is President of the Center for Science in the Public Interest. Previously, Lurie was the Associate Commissioner for Public Health Strategy and Analysis at the Food and Drug Administration, where he worked on antimicrobial resistance, transparency, caffeinated beverages, arsenic in rice, fish consumption by pregnant and nursing women, expanded access to investigational drugs, and prescription drug abuse. Prior to that, he was Deputy Director of Public Citizen's Health Research Group, where he addressed drug and device issues, coauthored the organization's *Worst Pills, Best Pills* consumer guide to medications, and led efforts to reduce worker exposure to hexavalent chromium and beryllium. Earlier, as a faculty member at the University of California, San Francisco and the University of Michigan, he studied needle exchange programs, ethical aspects of mother-to-infant HIV transmission studies, and other HIV policy issues domestically and abroad.

Chairman FOSTER. Thank you. And our next witness is Dr. Finigan, now recognized for 5 minutes.

TESTIMONY OF DR. JAMES FINIGAN,
DIRECTOR OF THE RESPIRATORY CENTERS
OF EXCELLENCE, NATIONAL JEWISH HEALTH

Dr. FINIGAN. Thank you. I would like to thank the Members of the Subcommittee for inviting me to speak on my experiences as a clinical investigator during the COVID–19 pandemic. I am a pulmonary and critical care physician at National Jewish Health in Denver, Colorado, where I see patients in our pulmonary clinic and intensive care units. National Jewish Health is the leading respiratory hospital in the Nation and is the only facility in the world dedicated exclusively to medical research and to the treatment of patients with respiratory, cardiac, immune, and related disorders. We work with several hospitals in Colorado, including our flagship St. Joseph Hospital, to provide pulmonary and critical care medicine and have established respiratory institutes in New York in partnership with Mount Sinai Health System and in Philadelphia with Jefferson Health.

I have close to two decades of basic, translational, and clinical research experience and currently help lead our COVID–19 clinical research program. Responding to this pandemic has required a complete reorientation of our clinical and research programs at National Jewish. Clinically, we reorganized our workforce and physical plant to diagnose and treat COVID–19 patients while simultaneously planning for the worst-case scenario. For our research operations, it meant halting existing studies and starting up new studies as quickly as possible, all with much of our staff working remotely. Many of these studies are basic science investigations to identify new targets for treatment.

At National Jewish Health, we've gone from zero COVID–19 clinical studies to 10 or more therapeutic trials in various stages of development over the past 12 weeks. Prior to embarking on any specific research study, each trial requires a number of time-consuming steps, including formal protocol review, assessment of our ability to perform the trial as designed, determination of any conflicts with ongoing trials, budget negotiation, and agreement on contracting terms. This process ordinarily takes 3 months or longer. During this crisis, we've been able to cut that time to a few weeks. For a pharmaceutical company or other study sponsor, this process must be repeated at every study site. As an example, the recently published remdesivir study had 60 sites.

And reflecting on our experience at National Jewish Health during this pandemic, I believe three points should be highlighted. First, to rapidly deploy clinical trials of new or repurposed drugs, a pre-existing, organized network of research sites is essential. The recently announced NIH-led ACTIV program is an example of this. ACTIV stands for Accelerating COVID–19 Therapeutic Interventions and Vaccines. It is a public-private partnership to create a collaborative framework for prioritizing vaccine and therapeutic candidates and streamlining clinical trials using existing clinical methods.

Another example is the Prevention and Treatment of Acute Lung Injury, or PETAL network. PETAL is an NIH-funded network of academic medical centers dedicated to studying acute lung injury and the acute respiratory distress syndrome, the disease caused by SARS-CoV–2. This network has been repurposed to study the clinical features and possible treatments of COVID–19. For the past month, the PETAL network developed and launched two research protocols, and both studies will likely be completed in the coming weeks. Networks like these can be used in collaboration with industry as a platform to launch quickly new studies on promising treatments.

Second, we need ongoing investigation of SARS-CoV–2 and COVID–19 to understand the virus and mechanisms of this disease. Much of this research will be what we call preclinical studies, bench research in cells and animal models to expand our understanding of COVID–19 pathophysiology. However, this can only exist if we maintain a robust national medical research mission and infrastructure.

Dividends from this kind of research are not always immediately apparent. However, a basic understanding of the underlying science of this disease will drive development of new therapeutics moving forward both for this pandemic and to prepare us for the next one. These studies can help identify which new drugs are most promising and can inform a rational strategy for prioritizing drugs for clinical trials.

Third, another pandemic is likely in our future. What that will be we don't know, but we should be planning now on how to incorporate a full research operation into any future pandemic response. I've been impressed with the research community reaction to this crisis. However, even with this effort, an organized national response was not launched until several months into the pandemic. Coordination of what research will be performed and how it will be executed, the respective roles of organizations such as the FDA, NIH, CDC, BARDA (Biomedical Advanced Research and Development Authority), as well as industry, should be considered prospectively. Research is as important to defeating this pandemic and being ready for the next one as personal protective equipment, intensive care units, and ventilators. Thank you.

[The prepared statement of Dr. Finigan follows:]

June 19th, 2020

James Finigan, M.D. Director of the Respiratory Centers of Excellence, National Jewish Health Denver, Colorado

Testimony to the Subcommittee on Investigations & Oversight of the House Committee on Science, Space and Technology.

Hearing: ***Repurposing Therapeutic Drugs for COVID-19: Research Challenges and Opportunities***

I thank the members of the sub-committee for inviting me to speak on my experiences as a clinical investigator during the COVID19 pandemic.

I am a pulmonary and critical care physician at National Jewish Health in Denver, Colorado where I see patients in our clinic and intensive care units. I have close to two decades of basic, translational and clinical research experience, and currently help lead our COVID19 clinical research program.

National Jewish Health is the leading respiratory hospital in the nation. Founded 120 years ago as a nonprofit hospital, National Jewish Health today is the only facility in the world dedicated exclusively to groundbreaking medical research and treatment of patients with respiratory, cardiac, immune and related disorders. National Jewish Health is a world leader in research on all facets of the lung, in both disease and health, as well as inflammation and immune function. Patients and their families come to National Jewish Health from around the world to receive cutting-edge, comprehensive, coordinated care. We work with several other hospitals in Colorado, including our flagship National Jewish Health-Saint Joseph Hospital, to provide pulmonary and critical care medicine and have established Respiratory Institutes in New York in partnership with Mount Sinai Health System and in Philadelphia with Jefferson Health.

COVID19 is the disease caused by infection with the SARS-CoV-2 virus. Most cases are mild but roughly 20% of patients develop pneumonia and at least 5% will develop respiratory failure, multi-system organ dysfunction and shock. The case fatality rate is roughly 2%. This is in comparison to seasonal flu which has a fatality rate of about 0.1%. Over 100,000 Americans have died of COVID19 in the past five months.

Responding to this pandemic has required a complete re-orientation of our clinical and research programs. Clinically, we reorganized our workforce and physical plant to diagnose and treat COVID19 patients while simultaneously planning for the worst-case scenario. For our research operations, it meant halting existing studies and starting up new studies as quickly as possible, all with much of our staff working remotely.

At National Jewish Health, we've gone from zero COVID19 related studies to ten or more therapeutic trials in various stages of development over the last twelve weeks. Prior to embarking on any specific research study, each trial requires a number of time-consuming steps including: formal protocol review, assessment of our ability to perform the trial as designed, determination of any conflicts with other ongoing trials, budget negotiation, Institutional Review Board review, response and approval, and agreement on contracting terms. This process ordinarily takes three months or longer. During this crisis, we have been able to cut that time to a few weeks. For a pharmaceutical company or other study sponsor, this process must be repeated at every study site. As an example, the recently published Remdesivir study had sixty sites.

In reflecting on our experience at National Jewish Health during this pandemic, I believe three points should be highlighted.

First, to rapidly deploy clinical trials of new or repurposed drugs, a pre-existing, organized network of research sites is essential. The recently announced, NIH-led ACTIV Program is an example of this. ACTIV stands for "Accelerating COVID19 Therapeutic Interventions and Vaccines" and is a public-private partnership to create a collaborative framework for prioritizing vaccine and therapeutic candidates and streamlining clinical trials using existing clinical networks. Another example is the Prevention and Treatment of Acute Lung Injury, or "PETAL," Network. PETAL is an NIH-funded network of academic medical centers dedicated to studying Acute Lung Injury and the Acute Respiratory Distress Syndrome, the disease caused by SARS-CoV2. This network has been repurposed to study the clinical features and possible treatments of COVID19. In the past month, the PETAL Network developed and launched two research protocols and both studies will likely be completed in the coming weeks. Networks like these can be used in collaboration with industry as a platform to launch new studies on promising treatments.

Second, we need ongoing investigation of SARS-CoV-2 and COVID19 to understand the virus and mechanisms of this disease. Much of this research will be what we call pre-clinical studies; bench research in cells and animal models to expand our understanding of COVID19 pathophysiology. These are foundation studies where candidate drugs and non-pharmacologic therapies will be identified. However, this can only exist if we maintain a robust national medical research mission and infrastructure. Dividends from this kind of research are not always immediately apparent, however a basic understanding of the underlying science of disease drives development of new therapeutics. This is true for this pandemic and will help prepare us better for the next one.

Third, another pandemic is likely in our future. What that will be, we don't know, but we should be planning now on how to incorporate a full research operation into in any future pandemic response. I have been impressed with the research community reaction to this crisis. However, even with this effort, an organized national response was not launched until several months into the pandemic. Coordination of what research will be performed and how it will be executed, the respective roles of organizations such as the FDA, NIH, CDC, as well as industry should be considered prospectively. Research will be as important to defeating this pandemic, and the next one, as personal protective equipment, intensive care units and ventilators.

Dr. Finigan is a pulmonary and critical care physician at National Jewish Health in Denver, Colorado where he serves as the Director of the Respiratory Centers of Excellence.

Dr. Finigan obtained his Bachelor of Arts in English from Colgate University in 1993. After graduating from medical school from the University of Rochester in 1999, he completed a residency in Internal Medicine at Case Western Reserve University in 2002 and was chosen as a Chief Resident in Internal Medicine for 2002-2003. He completed a fellowship in Pulmonary and Critical Care Medicine at Johns Hopkins University in 2007.

Dr. Finigan has two decades of basic, translational and clinical research experience. he began my research training at Johns Hopkins in 2003. He has a basic science laboratory that focuses on lung endothelial and epithelial biology and mechanisms of lung injury and lung cancer. He has received research funding from the National Institutes of Health, as well as a variety of foundation and industry sponsors. He conducts clinical research in lung cancer, acute lung injury and the acute respiratory distress syndrome. He also serves as the Medical Director of the Lung Cancer Screening Program. Clinically, he sees patients in the outpatient clinic and intensive care units.

Chairman FOSTER. Thank you. That was beautifully timed. The Chairman appreciates the accuracy of your time estimate and will now recognize Dr. Stevens for 5 minutes. Whoops, Rick, mute.

TESTIMONY OF DR. RICK L. STEVENS,
ASSOCIATE LABORATORY DIRECTOR
FOR COMPUTING, ENVIRONMENT AND LIFE SCIENCES,
ARGONNE NATIONAL LABORATORY

Dr. STEVENS. OK. I thought they were going to unmute me. So, thank you, Chairman Foster, Ranking Member Lucas, and Members of the Subcommittee, for inviting me here to talk about our work relating to COVID–19. My group and collaborators work primarily in the development of methods for high-performance computing and artificial intelligence applied to problems in biology and medicine, so let me talk a little bit about what we're doing.

I should say that I'm speaking for Argonne, myself and for Argonne. I'm not speaking for the Department of Energy. My work focuses on applying high-performance computing methods to problems in science and medicine, and I've worked in this combination space for over 25 years. And related to COVID–19, I'm the co-PI (principal investigator) on a DOE, *CARES Act*-funded, nine-laboratory consortium project that is working on molecular design for COVID. As part of that effort, we're looking at repurpose-able drugs, as well as de novo compounds.

Now, let me tell you a little bit about the virus and why it—why this drug search process is actually challenging. The virus is a single-stranded RNA (ribonucleic acid) virus. It codes for about 30 proteins. About 2/3 of those proteins commandeer host cell machinery to make copies of the virus, and about 1/3 of them are involved in packaging and formulating the virus. Of those proteins, there's perhaps 10, maybe a little bit more than that in the virus that the virus codes for that are plausible drug targets. The virus proteins also interact with the host. Perhaps as many as 300 protein interactions appear to occur, and a number of those host proteins could also be drug targets.

Now, it's also important to know this virus is very closely related to SARS–1, and so since around 2003 the scientific community has had access to information about its genome and its proteome and has been working on this. And thanks to the DOE light sources and light sources elsewhere, we have very detailed atomic structural maps of these proteins, and in the last few months we've acquired more of these structural maps. But what's not known is essentially how existing drugs interact with these virus targets. That has not been the subject of large-scale computational work prior to now and has not been the study of large-scale experimental work.

So, what I'm working in and my collaborators at the University of Chicago and at the nine national laboratories that are collaborating with us are really looking at how we can apply high-performance computing to scan not only the 2,500 or so licensed drugs worldwide and the 7,000 or so drugs that are in the pipeline but literally billions of molecules that we know can exist.

Now, in this effort, it's also critical to recognize the three main infrastructures that we're using. We're using supercomputers, the fastest machines in the world that exist at the DOE labs like at

Argonne and at Oak Ridge. The famous Summit computer at Oak Ridge is a workhorse for us but also machines that the NSF supports. We also use the light sources. These are critical for determining structures of proteins and for determining structure with molecules, potential inhibitors, bound into these proteins so we can understand their mechanism of action.

And the third resource that's critical for this effort is the NIH-funded biocontainment laboratories, the regional biocontainment laboratories that were stood up after 9/11, after the scare—after the anthrax scare and concern about emerging pathogens, and these exist at various locations in the country. The one that is close to me is the H.T. Ricketts lab operated by the University of Chicago here at Argonne. We're also using the Regional Biocontainment Laboratory that's at the University of Tennessee Health Sciences Center. Those centers are critical because they can work on active virus, virus that's—viruses are not alive, but viruses where we can look at the entire lifecycle and whole cell assays and animal-based assays.

So, essentially, what our program is, is to use the computers to search for molecules, including all the repurposing drugs. They get scored on each individual molecular target. The drugs that appear to have high potential get forwarded to our experimental collaborators where they get assayed biochemically and then ultimately through whole cell assays.

I should point out one more thing. There's lots of advice we could give about future pandemics, but one thing that's holding us back, that's holding back the scientific community right now is the lack of biochemical assays for these specific virus protein functions. The National Institutes of Health are investing in development of these assays. They have the NCATS (National Center for Advancing Translational Sciences) program working on that. The national laboratories are also investing in assay development, but that is a major bottleneck. In the future, we need to invest in assays up front. They need to be stockpiled. They should become part of the national critical infrastructure and made available to these biocontainment laboratories so that, in the future, rapid screening can happen on any new outbreak. And I'll leave it at that. Thank you.

[The prepared statement of Dr. Stevens follows:]

Testimony of Rick Stevens
Associate Laboratory Director
for Computing, Environment and Life Sciences
Argonne National Laboratory

Before the
Subcommittee on Investigations and Oversight
Committee on Science, Space and Technology
U.S. House of Representatives

"Repurposing Therapeutic Drugs for COVID-19: Research Challenges and Opportunities"

June 19, 2020

Chairman Foster, Ranking Member Norman, and Members of the Subcommittee, thank you for the opportunity to participate in today's discussion about Drug Repurposing for COVID-19 and the role of the U.S. Department of Energy (DOE) National Laboratories.

I am Rick Stevens, the Associate Laboratory Director responsible for Computing, Environment and Life Sciences research at Argonne National Laboratory and a Professor of Computer Science at the University of Chicago. My research focuses on finding new ways to advance science and health outcomes using computation. This includes helping to develop the Exascale computing initiative and the emerging AI for Science initiative in the DOE. Currently I lead research projects that are developing and using High-Performance Computing (HPC) and Artificial Intelligence (AI) in infectious diseases, cancer and in other areas of science.

I have been associated with the DOE national laboratory system for nearly forty years. My testimony today is on behalf of my work at Argonne National Laboratory and does not represent the views of the Department of Energy.

Let me start by telling you a bit about the virus we are fighting.

The virus is called **SARS-CoV-2,** and the disease it causes in humans is called **COVID-19**.

The SARS-CoV-2 virus is a coronavirus closely related (> 90% similar) to the SARS and MERS coronaviruses that emerged in 2003 and 2012 and is more distantly related (50% similar) to the coronaviruses that cause the common cold.

Its natural host is a bat.

There is no evidence to suggest it was engineered.

The virus was probably transmitted to humans via an intermediate host similar to SARS (civet) and MERS (camel), but we currently don't know precisely what species that intermediate animal was.

Globally, the biomedical community has sequenced and analyzed over 30,000 genome sequences of the SARS-CoV-2 virus, and while there are some differences between samples (isolates), they are minor and do not seem to give rise to significant differences in virulence or mortality.

The SARS-CoV-2 virus (like all viruses) is not alive.

It cannot replicate outside of the host and is dependent entirely on the host to complete its replication cycle.

The particle of the virus is quite small, on the order of 100nm in diameter or about 1000th the thickness of a human hair and is not visible to the human eye.

In this very small volume, the virus packs a single-stranded RNA genome that codes for about 30 proteins.

Of those 30 proteins, about two-thirds of them are used to commandeer the host cell into helping it replicate. The other proteins are used to package the viral RNA and build the virus structure. Some proteins have multiple functions.

Each infected host cell produces about 1000 new virus particles in about 10 hours.

Of the 30 proteins in the virus genome, about 10 of them are plausible drug targets.

Thanks to the work at the light-sources of the DOE national laboratories and elsewhere, we have good atomic level structures for most of these proteins. In fact, most of these proteins are highly similar to the proteins from the SARS 1 virus. The SARS 1 virus has been studied by a small global research community for over a decade and these research results provided a critical head-start to understanding SARS-CoV-2.

The virus proteins also interact with many human proteins. Some virus proteins turn off functions in the host that would normally help recognize the virus and would then activate aspects of the immune system. In other cases, the viral proteins regulate host processes to help create a more suitable environment for the virus to replicate.

All told, perhaps 200-300 host proteins are involved in some form of interaction with the virus proteins, and some of those (perhaps 10-20) are plausible drug targets.

Globally, there are about 2500 drugs that are approved by national authorities and are generally available in the marketplace.

These existing "potentially repurposable drugs" are obvious candidates for consideration for therapeutics for COVID-19 since they have already passed through numerous tests for safety and side effects, and the dosing for human use is reasonably well understood.

What is not deeply understood (certainly not at the beginning of this pandemic) is which of these existing "on the market" drugs are active against targets in the virus or host to treat COVID-19.

I am personally involved in research projects that are actively working on discovering small molecule antiviral drugs for COVID-19, which include repurposing existing drugs. Resources for these efforts come from NIH and the Department of Energy, including crucial support under the CARES Act.

My research partners include teams at the University of Chicago and a nine-laboratory consortium of DOE laboratories (Argonne, Oak Ridge, Berkeley, Brookhaven, Livermore, Los Alamos, Pacific Northwest, Sandia, and SLAC).

In these collaborations, my role has been to lead the efforts to using large-scale computing and artificial intelligence to identify existing drugs and new compounds for treating COVID-19.

I have a wonderful team of about 100 people across many institutions deeply engaged in different aspects of the computational effort.

To address the challenge of therapeutics development for COVID-19 requires the creation of interdisciplinary teams of scientists that include physicians, virologists, synthetic and medicinal chemists, molecular biologists, biochemists, structural biologists, computational biologists, bioinformaticians, computer scientists, data scientists, drug designers, molecular engineers, and AI researchers.

These teams started forming in March 2020 when it became clear that COVID-19 was becoming a pandemic.

Our early goal was to use computational screening of existing drugs to quickly determine candidates for experimentation, and to get those priority hits into the experimental pipelines as fast as possible. To give you a sense of the urgency, in some cases, our UChicago colleagues synthesized molecules in house since it was faster than ordering them.

Once those initial screens were underway, we started focusing on and are continuing a longer-term effort to investigate new compounds prioritized specifically for effectiveness on COVID-19 related targets.

In conducting this work, we are using three significant classes of national user facilities:

1. **The DOE and National Science Foundation (NSF) supercomputers:** Argonne Leadership Computing Facility (ALCF), Oak Ridge Leadership Computing Facility (OLCF), National Energy Research Scientific Computing Center (NERSC), Lawrence Livermore National Laboratory (LLNL), Texas Advanced Computing Center (TACC), San Diego Supercomputer Center (SDSC), Pittsburgh Supercomputing Center (PSC), National Center for Supercomputing Applications (NCSA), etc.

These supercomputers are being used to model virus proteins, protein interactions, virtual drug screening and to build and run AI models to predict binding and other properties of potential drugs.

2. **The DOE supported x-ray light sources and neutron sources:** Advanced Photon Source (APS) at Argonne, Advanced Light Source (ALS) at Lawrence Berkeley, Stanford Synchrotron Radiation Light Source (SSRL) at SLAC, National Synchrotron Light Source II (NSLS II) at Brookhaven, and Spallation Neutron Source (SNS) at Oak Ridge National Laboratories.

The light-sources and neutron source are used to determine structures of proteins, protein complexes and the position and orientation of drugs bound to the active sites in proteins.

And critically the:

3. **National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) supported Biocontainment Laboratories (Biosafety Level 3):** the Howard T Ricketts Laboratory operated by the University of Chicago and the University of Tennessee Health Science Center Regional Biocontainment Laboratory, where experimental screening on active "live" virus can take place.

The biocontainment laboratories are critical since without them we are limited to working only on biochemical assays and not full virus replication assays.

At Argonne National Laboratory we have developed and published a database of over 4 billion known compounds from many sources and the associated information to support Artificial Intelligence methods to accelerate computational screening. Over 2 million hours of computer time were used to build this database.

We have also identified a priority library of about 10 million molecules that are readily available for experimental validation. This library has been used to screen drug targets and to identify priority compounds that can be quickly acquired for experimental validation.

My team is using the world's fastest supercomputers housed at DOE Leadership Computing Facilities at Argonne and Oak Ridge National Laboratories, and other machines across the country, to virtually screen these 4 billion compounds on dozens of COVID-19 drug targets. This is something that would not have been possible just a few

years ago and is not possible without the advances in AI and machine learning, supported by the DOE's Office of Science

These computational efforts have been ongoing for several months now and hundreds of top scoring molecules (including many drug repurposing candidates) have been experimentally screened for antiviral activity, and thousands more are in the pipeline for experimental screens.

An important point to make here is that while repurposing is a fast route to possible treatments, in general, the repurposing candidates are not the ideal molecules to bind to COVID-19 specific targets.

Long-term, it is highly likely that the most effective drugs for treating COVID-19 will need to be purpose built, and this will take time and longer-term investment.

Our goal in the short term is to try to do as much up-front work as possible on these molecules so that the private sector—that would ultimately need to produce new or repurposed drugs—has reasonable places to start.

We want to provide candidate lead compounds that have demonstrated activity on important COVID-19 targets.

A few observations on how well this is going and some recommendations for the future:

- The national research community is working well together and has quickly identified and integrated capabilities from DOE, NIH, and many universities to fight COVID-19.
- The DOE has created a National Virtual Biotechnology Laboratory effort, supported by CARES Act funding, that is coordinating COVID-19-related efforts at all the DOE labs; this is working well.
- Interagency communication paths are open and senior leaders at the agencies are coordinating.
- The national laboratory efforts are coordinating with Pharma and have ongoing conversations about methods and potential hand offs on drug candidates.

As these national collaborations continue and we look to continue to make an impact in addressing COVID-19 and future potential pandemics, I offer a few considerations and recommendations for going forward:

- Experimental assay development needed to validate drug repurposing candidates is difficult and time consuming and is a bottleneck for antiviral drug development efforts. These assays should be a high-priority part of long-term research programs and considered critical national infrastructure.

- Once assays exist for a new target, baseline experimental screens of existing drugs can be done relatively quickly, inexpensively, and in parallel with

computational work and would provide important datasets for AI efforts. Standing libraries of repurposing compounds are available and should be part of standard inventory at regional biocontainment laboratories.

- The national network of research capabilities that has been assembled to address the COVID-19 challenge should be maintained and tuned for future epidemics and emerging pathogens. Modern therapeutics development needs tight integration of high-throughput experiments, structure determination, assay and methods development, data analysis, AI, and simulation.

- Standing interagency agreements should be put in place to streamline funding transfers, materials transfers, personnel exchange, and data sharing. Certainly DOE, NIH, NSF, DOD all have capabilities that need rapid coordination and access. A collaboration network is needed to exercise these connections on an ongoing basis.

Finally, SARS-CoV-2 and COVID-19 is not the first pandemic and it is not likely the last one we will see. Zoonotic diseases (those that originate in animals and infect humans) are likely to become more common as the pressures of economic and social development and land use changes push larger human populations deeper into traditionally unsettled areas and cause more human contact with diverse animal species.

I believe we need a systematic approach to sampling and understanding the diversity of pathogens carried by animals in natural environments and to use this information to understand the likelihood of transition to human hosts, their pathology, and to get a head start on therapeutics, and in general to be more prepared for the next outbreak.

We should be mounting internationally coordinated expeditions to sample the many thousands of known carrier species for microbial pathogens and use this information to manage risk.

The cost of proactive risk management for emerging pathogens will be orders of magnitude less than the cost of another pandemic and the tragic loss of life.

The DOE laboratories exist to do the science and to create technology for the national grand challenges. As organizations they are specifically designed to support fast moving, interdisciplinary science, precisely the kind of science that is needed to respond to national challenges like COVID-19.

Looking forward I believe we should consider how to structure a permanent role for the National Laboratories to augment and support the national response to future infectious disease challenges.

Thank you. I would be happy to answer any questions you or other members of the committee may have.

Bio: Rick Stevens is the Associate Laboratory Director of the Computing, Environment and Life Sciences Directorate at Argonne National Laboratory, and a Professor of Computer Science at the University of Chicago, with significant responsibility in delivering on the U.S. national initiative for Exascale computing and developing the DOE initiative in Artificial Intelligence (AI) for Science.

His research spans the computational and computer sciences from high-performance computing, to the building of innovative tools and techniques for biological science and infectious disease research as well approaches to advance deep learning to accelerate cancer research. He also specializes in high-performance computing, collaborative visualization technology, and grid computing. Currently, he is the PI of the Bacterial / Viral Bioinformatics Resource Center (BV-BRC) which is developing comparative analysis tools for infectious disease research and serves a large user community; the Exascale Deep Learning and Simulation Enabled Precision Medicine for Cancer project through the Exascale Computing Project (ECP), which focuses on building a scalable deep neural network application called the CANcer Distributed Learning Environment (CANDLE); the Predictive Modeling for Pre-Clinical Screening (Pilot 1) of the DOE-NCI Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) project; and the Co-design of Advanced Artificial Intelligence (AI) Systems project focused on predicting behavior of complex systems using multimodal datasets.

At Argonne, he is leading the Laboratory's AI for Science initiative and currently focusing on high-performance computing systems which includes collaborating with Intel and Cray to launch Argonne's first exascale computer, Aurora 21, as well as leading a partnership with Cerebras Systems to bring hardware on site to advance the deep learning experiments being pursued at Argonne for basic and applied science and medicine with supercompute-scale AI.

Prof. Stevens is a member of the American Association for the Advancement of Science and has received many national honors for his research, including an R&D 100 award.

Chairman FOSTER. Well, thank you. Well, at this point we'll begin our first round of questions, and the Chair will recognize himself for 5 minutes here.

Dr. Rome and Dr. Lurie, you know, there have been—there's been mention of the—what is being set up in Europe and internationally and as opposed to what has happened in the United States in terms of the coordination of the large number of clinical trials. Can either of you say little bit about what we get right that's gotten—you know, that's better or worse than what's done in other countries and other international collaborations and whether we're insufficiently or more than—or sufficiently connected to those?

Dr. LURIE. Let me let Mr.—Dr. Rome answer because, sir, I think you neglected to give him the chance to read his statement.

Chairman FOSTER. Oh, goodness. My apologies. My apologies. Thank you, Dr. Rome. I was fumbling multiple windows here and neglected, so—and thank you for that, Dr. Lurie.

All right. Dr. Rome, you're now recognized for 5 minutes.

TESTIMONY OF DR. BENJAMIN ROME,
ASSOCIATE PHYSICIAN, BRIGHAM AND WOMEN'S HOSPITAL;
POSTDOCTORAL RESEARCH FELLOW,
HARVARD MEDICAL SCHOOL

Dr. ROME. Thank you. Sorry about that. So, Chairman Foster, Ranking Member Lucas, and Members of the Subcommittee, thank you for inviting me. I'm a practicing primary care physician and a health policy researcher at Harvard Medical School and Brigham and Women's Hospital in Boston. I'm a member of the division of pharmacoepidemiology and pharmacoeconomics and the Program on Regulation, Therapeutics, and Law for PORTAL, an interdisciplinary research group that studies prescription drug development, regulation, use, and cost. I am honored to be here today to talk with you about the process for studying and approving repurposed drugs during the COVID–19 pandemic.

Drug development can be a lengthy process, and repurposing several medications with existing data about safe use in humans allowed clinical trials to begin early in the pandemic. As a result, just 4 months after the first COVID–19 patient was reported in the United States, several high-quality clinical trials have provided solid evidence relating to at least four drugs, two of which have proven effective: dexamethasone, a low-cost generic corticosteroid that can be readily prescribed by clinicians; and remdesivir, an antiviral that has not yet been approved for any indication by the FDA but is now available under an emergency use authorization.

However, we have also witnessed examples of how the process for testing and approving drugs can go awry, as exemplified by the case of hydroxychloroquine. We should learn from our past missteps as we move forward, and our experiences so far suggest four key actions Congress should take.

First, Congress should hold all government agencies and officials accountable for making statements and acting based on the best available scientific evidence. Hydroxychloroquine was widely touted by President Donald Trump and was issued an emergency use authorization by the FDA based on preclinical and limited anecdotal evidence that turned out to be unreliable. These actions led to

widespread use of the drug, which exposed patients to risk, led to shortages at pharmacies, and diverted attention and resources that might have been dedicated to other potential therapies.

Second, Congress should invest heavily in high-quality clinical trials which are necessary for determining whether drugs are safe and effective. Notably, most of the high-quality evidence generated so far during the pandemic has resulted from public funding, including the U.S. Government in the case of remdesivir and the United Kingdom Government in the case of dexamethasone.

While the pharmaceutical industry will continue to have a role to play, the Federal Government's leadership and involvement are crucial, particularly for repurposed drugs which industry may have little or no financial incentive to study. However, such public investment should be made with the assurance that any medications that are found effective will be priced fairly and distributed equitably to patients who need them. No American should be prevented from accessing potentially lifesaving treatment for COVID–19 due to cost.

Third, Congress should invest in a public health infrastructure and national clinical trial network that can help shape the research agenda, facilitate research across multiple sites, and limit duplicative efforts. In several European countries, government and academics have collaborated on large clinical trials that test multiple repurposed drugs simultaneous. A prime example is the RECOVERY Trial based out of the University of Oxford. This trial has already provided useful information about the lack of effectiveness of hydroxychloroquine and the effectiveness of dexamethasone.

Finally, Congress should amend the process by which the FDA issues emergency use authorizations or EUAs. The level of evidence required to meet the standard of an EUA should be clarified. And to increase transparency, Congress should compel the FDA to make all related data public at the time that the EUA is issued.

As new evidence emerges, the FDA should be directed to apply the same standards for revoking an EUA as was required for issuing it. EUAs should be accompanied by a clear and transparent plan for how the drug will be fairly and equitably distributed to patients, something that was lacking for both hydroxychloroquine and remdesivir.

Finally, issuance of an EUA should be accompanied by collection of data on treated patients to gain additional insight about the drug's safety and effectiveness.

Our experiences so far studying repurposed drugs during the COVID–19 pandemic have shown that we need not choose between rigorous scientific evidence and speed. We can have both. As our fight to control the COVID–19 pandemic continues, Congress must assure that we uphold a drug approval process that follows the science and promotes the practice of evidence-based medicine.

In a recent viewpoint published in the *New England Journal of Medicine*, Dr. Jerry Avorn and I argued that, quote, "The health of individual patients and the public at large will be best served by remaining true to our time-tested approach in clinical trial evidence and drug evaluation." Thank you.

[The prepared statement of Dr. Rome follows:]

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Drug Approval During the Covid-19 Pandemic: Following the Evidence

Testimony of:

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United States House of Representatives
Committee on Science, Space, and Technology
Subcommittee on Investigations & Oversight
Friday, June 19, 2020
Washington, D.C.

Summary of Major Points

- Repurposing existing therapeutic agents allows opportunities for expedited clinical trials, and if found safe and effective, repurposed medications can be inexpensive and widely available options to treat patients with Covid-19.
- The pandemic has made it possible for high-quality clinical trials of potential therapies to be performed swiftly, due to a large volume of available patients to enroll and short disease course that allows for speedy measurement of important clinical outcomes.
- Observational studies based on real-world data can be a powerful, efficient tool to provide preliminary or additional evidence complementing clinical trials, but these studies must be high quality and methodologically rigorous.
- Most of the important evidence about which repurposed drugs are effective in Covid-19 has been publicly funded, and government funding is particularly important for repurposed drugs for which financial incentives for industry may be limited.
- Even before approving drugs, during a public health emergency the FDA has broad authority to authorize use of medications based on preliminary evidence.
- **Learning from our experience so far, Congress should take four actions to improve the process for studying and approving repurposed drugs moving forward.**
  1. Hold all government agencies and officials accountable to make statements and act based on the highest-quality available evidence; patients and providers rely on this information to guide evidence-based clinical practice.
  2. Further invest in research, either directly or through collaboration with academic institutions, and assure that drugs which receive federal funding will be priced fairly and made available equitably.
  3. Establish a centralized public health infrastructure and clinical trial network that can allow the federal government to take the lead on setting the research agenda, streamlining trials across multiple sites, reducing duplicative efforts, and improving the speed at which clinical trials can be performed.
  4. Make several improvements to the FDA's Emergency Use Authorization (EUA) process, including:
     - Clarifying and standardizing the level of evidence required to support an EUA, including the potential role of high-quality observational studies.
     - Increasing transparency by requiring all data informing the EUA be made publicly available at the time it is issued.
     - Outlining a robust plan for fair and equitable distribution of the product subject to the EUA and for negotiation with the product's manufacturer for a fair price.
     - Requiring ongoing collection of patient outcome data to support a product's safety and effectiveness while the EUA is in effect and the product has not yet been approved by the FDA.

Chairman Foster, Ranking Member Norman, and Members of the Investigations and Oversight Subcommittee:

My name is Benjamin Rome. I am a practicing primary care physician and a health policy researcher at Harvard Medical School and in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital in Boston. Within the Division, I am a member of the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research group that studies the intersections between prescription drug affordability and use, laws and regulations related to medications, and the development and cost of drugs. I am honored to be here today to talk with you about the process of studying and approving drugs during the Covid-19 pandemic, with a focus on the best way to evaluate existing medications that might be repurposed to treat patients during this public health emergency.

Drug Approval During Covid-19

The global Covid-19 pandemic has kicked of an urgent search for effective therapies and has put pressure on the US Food and Drug Administration (FDA) to swiftly make medications available to patients. The need to act expeditiously has also encouraged us to consider whether existing medications that we already have experience using for different indications might be repurposed and tested for effectiveness in treating Covid-19. Even remdesivir – an experimental antiviral drug that was recently shown to be effective in Covid-19[1] – was initially developed to treat hepatitis C and was subsequently tested unsuccessfully in patients with Ebola before being repurposed during the current pandemic.[2] Drug development can be a lengthy process, in which human clinical trials are only the final step. Thus, the decision to repurpose several drugs that have existing data in humans allowed clinical trials to begin early in the pandemic. Even prior to Covid-19, repurposing drugs for new indications was common. Among 26 transformative drug products or drug classes approved by the FDA from 1984-2009, our group found that 35% were repurposed after being initially studied for a different indication.[3]

In many ways, the search for Covid-19 therapies can already be considered a success. Just 4 months after the first patient with Covid-19 was reported in the US, two repurposed drugs have now demonstrated efficacy for treatment of Covid-19 and are available for use by US patients: remdesivir and dexamethasone.[1,4] Remdesivir use is now allowed under an FDA

Emergency Use Authorization (EUA), and dexamethasone is a low-cost generic corticosteroid that can readily be prescribed by clinicians.

However, our nation's response to Covid-19 has also shown examples of how the process for testing and approving drugs can go awry, as illustrated in the case of hydroxychloroquine.[5] Early studies showed that the hydroxychloroquine had in-vitro activity against the virus that causes Covid-19,[6] spurring interest in potentially repurposing the drug for use in Covid-19. In mid-March 2020, a small study of 36 patients in France reported that those who received hydroxychloroquine, particularly in combination with the antibiotic azithromycin, had faster clearance of the virus based on nasopharyngeal samples, compared to untreated controls.[7] The study was subsequently criticized for obvious methodologic flaws, including baseline differences between the treated and control patients, substantial amounts of missing data, and exclusion of patients who did not complete the study due to side effects or death.[8]

However, shortly after this study was published, President Donald Trump stated that hydroxychloroquine and azithromycin could be "one of the biggest game changers in the history of medicine."[9] He continued to advocate heavily for use of the drug and even claimed to have taken it himself to prevent Covid-19[10] despite no evidence that the drug was effective for that purpose. On March 28, the FDA issued an Emergency Use Authorization (EUA) for hydroxychloroquine and the related drug chloroquine for use among patients with Covid-19. The scope of the EUA was limited to permitting distribution of 30 million doses that were donated by the drug's manufacturer to the US Strategic National Stockpile.[11,12] However, the EUA was widely yet incorrectly reported by President Trump and others to mean that the FDA had approved the drugs for Covid-19.

Because hydroxychloroquine was already approved for use in patients with rheumatoid arthritis and lupus, it was easily available for clinicians to prescribe it "off label" to treat or prevent Covid-19, and demand for the drug spiked immediately after President Trump's initial endorsement.[13] This led to widespread shortages at pharmacies, which resulted in difficulty obtaining the medication among patients with rheumatoid arthritis and lupus, two conditions in which hydroxychloroquine has been shown to have benefits that outweigh its risks.[14] By contrast, there were concerns raised about the drug's known cardiac toxicities, particularly because there was not yet any convincing evidence of benefit when using the drug to treat Covid-

19, as well as concerns about accidental poisonings among patients who confused the drug with non-medical chloroquine-containing products.[13] In response to these concerns, on April 24 the FDA issued a warning cautioning against the use of hydroxychloroquine to treat Covid-19 outside of a hospital or clinical trial setting,[15] though the EUA remained in effect.

Ultimately, more evidence about the risks and benefits of hydroxychloroquine in patients with Covid-19 emerged. Two larger observational studies of several thousand patients in New York found no association between use of hydroxychloroquine and improved clinical outcomes.[16,17] In early June 2020, results were reported from two large randomized controlled trials finding that hydroxychloroquine was not effective either for preventing Covid-19 symptoms after exposure to the virus or for treatment of hospitalized patients with confirmed Covid-19.[18,19] Ultimately, the FDA withdrew the EUA for hydroxychloroquine on June 15.[20]

Maintaining Rigorous Standards for Evidence

The case of hydroxychloroquine highlights the importance of focusing attention and resources on rigorous, high-quality evidence to determine whether potential treatments are safe and effective. All drugs marketed in the US must be deemed to have "substantial evidence" of safety and effectiveness by the FDA.[21] While the FDA traditionally preferred two high-quality randomized controlled trials in which a drug is compared to placebo and patients and investigators are blinded to treatment assignment, this standard has been eroded over the past few decades. More recently, the FDA frequently determines that drugs meet the "substantial evidence" standard based on more limited evidence, especially if the drug treats a disease that is life-threatening or rare or when there is an unmet medical need.[21] Over the past several decades, the FDA has approved an increasing proportion of drugs through expedited approval pathways, with 81% of newly-approved drugs benefiting from at least one such pathway in 2018.[22] As a result, many drugs are now deemed safe and effective by the FDA based on a single clinical trial, trials with suboptimal design (e.g., lacking randomization or blinding), or trials that rely on surrogate outcome measures (such as changes to lab tests or radiology findings) which may or may not predict actual clinical benefit for patients.[22]

While it is tempting to believe that the FDA should rely on limited evidence given the urgent need for effective Covid-19 therapies, it would be a mistake to abandon the process of

carefully evaluating medications that has served us so well for many decades. In fact, the pandemic presents several conditions needed to expeditiously obtain rigorous clinical trial evidence. First, the entire global scientific community is united around finding treatments for Covid-19, with increased resources directed toward streamlining the regulatory and ethical review processes to prevent delays. The first randomized controlled trial began enrolling patients in China just one week after the virus had been identified.[23,24] As of May 11, 2020, there were 144 active clinical trials of therapeutic agents to treat Covid-19,[25] including several international trials testing multiple potential therapies at once.[4,26]

Second, the thousands of patients presenting each day to emergencies rooms and hospitals for treatment of Covid-19 allows for rapid enrollment into clinical trials, and patients have been very willing to participate. In the key clinical trial of remdesivir, 96% of the 1,107 patients assessed for eligibility were enrolled and randomized, an impressive feat for a trial of an experimental therapy versus placebo.[1] Third, because Covid-19 is an infectious disease with rapid progression or recovery, important clinical outcomes such as death, hospitalization, and need for a ventilator, can be quickly measured and used to judge the effectiveness of treatments.

Finally, once effective therapies are identified, FDA can expedite its regulatory review and quickly get the medication into the hands of doctors and patients. The FDA created a Coronavirus Treatment Acceleration Program to assist manufacturers in navigating regulatory requirements to and assure an expedited review process for any Covid-19 therapies that did prove effective.[25]

Thus, several aspects of the pandemic make it more feasible than ever to expeditiously conduct high-quality, rigorous randomized clinical trials that provide the best possible evidence of whether therapies are safe and effective. So far, this process has identified two drugs that either shorten duration of symptoms or reduce the risk of death in patients with Covid-19 – remdesivir and dexamethasone.[1,4] Trials of other drugs, including hydroxychloroquine and the antiviral combination lopinavir-ritonavir, have provided useful evidence that those drugs are *not* effective.[18,19,23]

Because many repurposed treatments are being used for routine care even prior to clinical trial results, researchers have attempted to use observational ("real world") data to provide early evidence about whether treatments are associated with improved outcomes. Large observational

studies, which use real-world patient data either from insurance claims or electronic health records, can provide early data when clinical studies are not feasible or have not yet been completed, and can offer complementary information to what is learned from clinical trials.[27–29] For example, clinical trials often do not include a sufficient number of patients to detect rare adverse effects, so observational data of thousands of patients can measure safety issues that were not noticed in the pre-approval clinical trials after drugs are approved by the FDA.[30] There is even evidence that observational data might be used confirm effectiveness of an existing mediation for a novel indication.[31]

However, observational research presents many potential methodologic challenges and must be performed well to assure validity of the results. For example, clinicians may reserve experimental Covid-19 therapies for the most severe cases, making it challenging to compare patients who received a drug to those who did not. Furthermore, certain key information may not be captured in available real-world databases. Nonetheless, research using these methods to study the safety and effectiveness of hydroxychloroquine and angiotensin-receptor blockers among Covid-19 patients has provided important preliminary evidence and informed clinical practice at the height of the pandemic.[16,17,32] While high-quality observational studies can provide useful evidence about use of repurposed drugs, the FDA should be not approve any new drug based on observational studies alone, without confirmatory evidence for clinical trials. Additionally, observational studies must be meticulously performed and rigorously vetted to assure that the data used is of high fidelity. Recently, both the *New England Journal of Medicine* and *The Lancet* issued retractions after concerns were raised about the provenance of a large international dataset used in these studies.[33,34] These retractions further underscore the importance of rigorous conduct and methodologic review of observational studies to assure that the results are reproducible and valid.

Opportunities for Federal Investment

While pharmaceutical companies are typically involved in development of new drugs, investment in research by the federal government also plays an important role. Federally funded basic and translational science were found to be related to every single new drug approved from

2010-2016. In addition, our group recently reported that publicly-supported research played a major role in the late-stage development 1 in 4 drugs approved over the last decade.[35]

Federal funding of research has played a critical role during the Covid-19 pandemic, and additional investment could expedite clinical studies necessary to learn whether drugs are safe and effective. This is particularly true for repurposed drugs, many of which are older and inexpensive, providing limited incentives for the for-profit brand-name pharmaceutical industry to study these drugs in Covid-19 patients. Indeed, the RECOVERY trial, which has already produced useful results for both hydroxychloroquine and dexamethasone, was funded by the United Kingdom's National Institute for Health Research.[4] But even when a drug is patent-protected, public investment has played an important role. While the intellectual property for remdesivir is owned by Gilead Sciences, the key clinical trial that has supported its use in Covid-19 was funded by the US federal government.[1]

By investing in clinical trials, the federal government can help expedite and prioritize the development of high-quality evidence to guide our use of therapeutics for Covid-19, particularly in the case of repurposed drugs. Furthermore, efforts in Europe have shown that a coordinated effort nationally across the health care system can result in expedited clinical trial results. Thus, by investing in a robust public health infrastructure and clinical trial network, the federal government could improve the US role in establishing a research agenda, facilitate collaborative research across multiple sites, and streamline efficiency by cutting down on duplicative efforts.

Improving Use of Medications Prior to FDA Approval

Naturally, during the pandemic there has been public demand to allow use of medications even before the FDA has had a chance to weigh the risks and benefits. There are several ways patients can access unapproved medications, with implications for the practice of evidence-based medicine.

First, medications that are already approved by the FDA and marketed for a different indication can be used "off-label" by physicians to treat Covid-19. While the FDA approves drugs for only those indications on which there is evidence of safety and effectiveness, clinicians can use the drugs for any indication within the realm of the practice of medicine. As a result, medications like hydroxychloroquine have been widely prescribed to patients even before

evidence had been collected about their safety and effectiveness. However, there is no rigorous tracking of clinical outcomes among patients prescribed drugs off-label, which limits our ability to use these experiences to learn about drugs' safety and effectiveness to guide evidence-based clinical decision-making.

Additionally, for investigational drugs that are not yet marketed, patients who are severely ill, lack alternative treatment options, and are not eligible for clinical trials may be eligible for "expanded access" programs.[36] The FDA nearly always grants permission for expanded access requests, and it is mainly up to manufacturers whether they will make their drug available to patients outside of clinical trials. This option was used for remdesivir, which Gilead provided to over a thousand Covid-19 patients outside of clinical trials.[37] Even before the Covid-19 pandemic, many conservative politicians and advocacy groups have supported expanding patients' "right to try" unapproved experimental medications.[38] This sentiment stems from an incorrect assumption that slow and onerous FDA requirements limit patient access to important and beneficial medications. To the contrary: the FDA approves the overwhelming majority of new drug applications it receives, with recent review times averaging less than one year and 6 months or less for truly innovative new treatments.[22] Currently, the FDA is one of the fastest and most efficient pharmaceutical regulatory agencies in the world, and a majority of drugs are approved in the US before being approved in Europe or Canada.[39]

Finally, during a public health emergency the FDA has broad regulatory authority to allow for use of unapproved drugs through Emergency Use Authorizations (EUAs). The FDA's authority to issue EUAs was first granted by Congress under the Project BioShield Act of 2004. While EUAs are typically used to allow rapid deployment and expansion of diagnostic testing and necessary devices (including personal protective equipment), the FDA can issue an EUA to allow use of a drug if it is "reasonable to believe" that the drug may be effective and the known and potential benefits outweigh the known and potential risks, based on "the totality of scientific evidence available."[40]

Prior to the Covid-19 pandemic, the only instance for which EUAs were used to permit use of medications for unapproved indications was during the 2009-2010 "swine flu" outbreak. At that time, an EUA was issued for use of peramivir – an investigational intravenous drug to treat influenza – in severely ill hospitalized patients with H1N1 influenza.[41] The EUA was based

on preliminary evidence from phase 2 and phase 3 clinical trials,[42] and the drug was given to approximately 1200-1500 patients, though there was no rigorous tracking of which patients received the drug or clinical outcome data.[43–45] Ultimately, a clinical trial showed that peramivir was not effective for treatment of severely ill hospitalized influenza patients, and the drug was approved by the FDA only for use in less sick, uncomplicated cases. Because the drug is administered intravenously and there are similar drugs from the same class that can be taken as pills (oseltamivir, also known as Tamiflu), the current use of peramivir is very limited.

During the current pandemic, the FDA has issued two EUAs for medications under two very different circumstances. The first, for hydroxychloroquine and chloroquine, was based on "limited in-vitro and anecdotal clinical data in case series," with no clear documentation of the specific evidence the FDA considered when making its decision.[42] Although the EUA was intended to increase access to the medications through use of the Strategic National Stockpile, the EUA instead signaled to providers that the drugs had been judged to be effective and—along with misleading statements by some politicians, celebrities, and media outlets—helped spur widespread off-label use that caused shortages of the drugs among patients who relied on them to treat rheumatoid arthritis and lupus.[14,42]

More recently, the FDA issued an EUA for use of remdesivir after preliminary clinical trial evidence found that the drug shortened duration of symptoms.[1] Because remdesivir is not yet approved or marketed in the US, the EUA provided a means for Gilead to begin distribution of the drug for use in US hospitals, which was kicked off by a donation of 1.5 million doses of the drug to the federal government. However, the process by which these doses of remdesivir was distributed was opaque, and it was not clear how the available supply of remdesivir was being equitably allocated to where it was most needed.[46] Furthermore, at the time the EUA was issued, the only publicly-available data to guide clinicians were top-line results from a press release; the full preliminary results were not published until 3 weeks later,[1] at which point distribution and use of remdesivir outside of clinical trial settings was already underway. Finally, because Gilead owns patents protecting remdesivir, they will be able to price the drug however they choose, and there has been no coordinated federal effort to negotiate a fair price based on the drug's value so that cost does not limit patient access.

Summary and Recommendations

The Covid-19 pandemic has highlighted both opportunities and challenges within the US drug approval process. Our use of repurposed medications has allowed rapid development and execution of several high-quality clinical trials, and we now have proof that such trials can feasibly be conducted in a short time frame. So far, trials have provided solid evidence relating to at least four potential drugs for Covid-19, of which two have proven effective. But along the way, there have been several missteps that we should learn from as we move forward and continue to study and develop therapies to treat and prevent Covid-19. Our experiences so far point toward four key actions Congress should take to improve the process by which existing drugs are repurposed and studied for use in Covid-19.

First, Congress should hold all government agencies and officials accountable for making statements and acting based on the best available scientific evidence. From the case of hydroxychloroquine, we have learned that promotion of a drug by politicians and explicit or implicit validation of a drug by government agencies based on limited evidence can have consequences. Scores of patients were exposed to the risks of hydroxychloroquine, which turned out not to be effective. Furthermore, the immense attention devoted to hydroxychloroquine over the past several months may have diminished resources that could have been dedicated to other potential therapies. The FDA's issuance of an EUA based on limited evidence and subsequent warnings about the drug safety sent mixed signals to patients and prescribers that caused confusion, hampered clinical trial enrollment, and may have diminished the public's trust. For its part, the scientific community must continue to scrutinize the quality and methodologic rigor of all published peer-reviewed research, as highlighted by recent retractions from two of the world's leading medical journals of studies that were based on flawed underlying data.

Second, Congress should invest heavily in the organization and conduct of high-quality clinical trials and observational studies, which we know can swiftly provide evidence for safety and effectiveness of therapies in Covid-19. Most of the highest quality evidence generated to date during the pandemic has resulted from public funding, including the US government in the case of remdesivir and the UK government in the case of dexamethasone. While industry will continue to play a role, the federal government's leadership and involvement are crucial, particularly for repurposed drugs for which industry may have little or no financial incentive to

conduct clinical studies. However, such public investment should be made with the assurance that any medications found effective will be priced fairly and distributed equitably to patients who need them. No American should be prevented from accessing a potentially lifesaving treatment for Covid-19 due to cost, especially when taxpayers fund the research supporting the drug's use.

Third, Congress should invest in in a public health infrastructure and national clinical trial network that allows for a coordinated response by shaping the research agenda, facilitating research across multiple sites, and limiting duplicative efforts. In several European countries, government and academics have collaborated on large, multi-site studies that test multiple repurposed drugs simultaneously. A prime example is the RECOVERY trial, which has already provided useful information about the lack of effectiveness of hydroxychloroquine and the effectiveness of dexamethasone. The Covid-19 pandemic is far from over, and investment in a similar infrastructure in the US can promote collaboration to expedite our ability to uncover additional therapies to treat or prevent Covid-19, including vaccines.

Finally, Congress should amend the process by which the FDA issues Emergency Use Authorizations (EUAs) to expand access to drugs before they are formally approved. The level of evidence and data required to meet the "reasonable to believe" standard should be made clearer, including the role of high-quality observational studies. While the EUA for hydroxychloroquine and chloroquine was based on "preclinical and limited anecdotal" evidence that turned out to be unreliable, the remdesivir EUA was not issued until there were clinical trial results. Any data the FDA uses should be described, and full results should be made publicly available at the time an EUA is issued. This was not the case for either EUA issued for drugs during the Covid-19 pandemic so far, and Congress could act to compel the FDA to increase transparency for all future EUAs. Additionally, as new evidence emerges, the FDA should be directed to apply the same standards for revoking an EUA as required for approving it; the hydroxychloroquine EUA lasted for 3 months despite multiple studies released during that time that raised questions about the drug's safety and effectiveness. Even while the EUA was in place, the FDA issued a warning cautioning against use of the drug due to serious cardiac risk. A more predictable set of rules around EUAs will promote public understanding, make it easier for physicians like me to know how to best treat patients, and enhance trust in government.

The issuance of an EUA should also be accompanied by a clear and transparent plan for how the drug will be fairly and equitably distributed to patients. It is not clear how the federal government allocated the doses of hydroxychloroquine or remdesivir that were provided by manufacturers or whether the EUAs satisfactorily improved access to either medication. Finally, issuance of an EUA should be accompanied by collection of demographic, treatment, and outcome information for all treated patients to gain additional insight about the drug's safety and effectiveness. A federal registry operated by the FDA or an independent third party could help find early safety signals not detected clinical trials, monitor for disparities in access to the drug, and expand upon effectiveness data from clinical trials. Failure to collect such information may hinder efforts to sufficiently understand a drug's safety and effectiveness to support FDA approval.

The Covid-19 pandemic has caused many to suggest that we must balance the desire for rapid use of experimental treatments against the need for rigorous evidence of drugs' safety and effectiveness. However, we have learned that we need not choose between rigorous scientific study and speed – we can have both. In a recent viewpoint published in *The New England Journal of Medicine,* Dr. Jerry Avorn and I argued that "The health of individual patients and the public at large will be best served by remaining true to our time-tested approach to clinical trial evidence and drug evaluation." As our fight to control the Covid-19 pandemic continues, Congress must assure that we uphold a drug approval process that follows the science and promotes evidence-based medical practice.

References

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *N Engl J Med*. 2020:1-12. doi:10.1056/nejmoa2007764
2. Eastman RT, Roth JS, Brimacombe KR, et al. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Cent Sci*. 2020. doi:10.1021/acscentsci.0c00489
3. Kesselheim AS, Tan YT, Avorn J. The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs. *Health Aff*. 2015;34(2):286-293. doi:10.1377/hlthaff.2014.1038
4. RECOVERY Trial Chief Investigators. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. Published 2020. Accessed June 16, 2020.
5. Rome BN, Avorn J. Drug Evaluation during the Covid-19 Pandemic. *N Engl J Med*. 2020;382(24):2282-2284. doi:10.1056/NEJMp2009457
6. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020;(Xx):1-8. doi:10.1093/cid/ciaa237
7. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020:105949. doi:10.1016/j.ijantimicag.2020.105949
8. Kim AHJ, Sparks JA, Liew JW, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. *Ann Intern Med*. 2020;(March):1-4. doi:10.7326/M20-1223
9. Trump D. Tweet Dated March 21, 2020. https://twitter.com/realDonaldTrump/status/1241367239900778501?s=20. Published 2020. Accessed June 16, 2020.
10. McCarthy T, Greve JE. Trump is taking hydroxychloroquine, White House confirms. *The Guardian*. https://www.theguardian.com/us-news/2020/may/19/trump-hydroxychloroquine-covid-19-white-house. Published May 19, 2020.
11. US Food and Drug Adminstration (FDA). Letter of Authorization: : Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease. https://www.fda.gov/media/136534/download. Published 2020. Accessed March 30, 2020.
12. US Department of Health and Human Services. https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html. https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html. Published 2020. Accessed June 16, 2020.
13. Liu M, Caputi TL, Dredze M, Kesselheim AS, Ayers JW. Internet Searches for Unproven COVID-19 Therapies in the United States. *JAMA Intern Med*. 2020;78:29-31.

doi:10.1001/jamainternmed.2020.1764
14. Alltucker K. "Medication I can't live without": Lupus patients struggle to get hydroxychloroquine, in demand for COVID-19. *USA Today*. https://www.usatoday.com/story/news/health/2020/04/18/hydroxychloroquine-coronavirus-creates-shortage-lupus-drug/5129896002/. Published April 18, 2020.
15. US Food and Drug Adminstration. FDA Drug Safety Communication, Safety Announcement [04-24-2020]. https://www.fda.gov/media/137250/download. Published 2020. Accessed June 18, 2020.
16. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment with Hydroxychloroquine or Azithromycin with In-Hospital Mortality in Patients with COVID-19 in New York State. *JAMA - J Am Med Assoc*. 2020;12203:1-10. doi:10.1001/jama.2020.8630
17. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020:1-8. doi:10.1056/nejmoa2012410
18. Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Engl J Med*. 2020:1-9. doi:10.1056/nejmoa2016638
19. RECOVERY Trial Chief Investigators. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19. Published 2020. Accessed June 16, 2020.
20. Hinton DM. Letter Revoking EUA for chloroquine phosphate and hydroxychloroquine sulfate. US Food and Drug Administration. https://www.fda.gov/media/138945/download. Published 2020. Accessed June 17, 2020.
21. US Food and Drug Adminstration (FDA) C. *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry*. Silver Springs, MD; 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products.
22. Darrow JJ, Avorn J, Kesselheim AS. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA - J Am Med Assoc*. 2020;323(2):164-176. doi:10.1001/jama.2019.20288
23. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. March 2020:NEJMoa2001282. doi:10.1056/NEJMoa2001282
24. Baden LR, Rubin EJ. Covid-19 - The search for effective therapy. *N Engl J Med*. 2020;382(19):1851-1852. doi:10.1056/NEJMe2005477
25. US Food and Drug Adminstration (FDA). Coronavirus Treatment Acceleration Program (CTAP). https://www.fda.gov/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap. Published 2020. Accessed June 16, 2020.
26. World Health Organization (WHO). "Solidarity" clinical trial for COVID-19 treatments. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-

novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. Published 2020. Accessed June 17, 2020.

27. Avorn J. In Defense of Pharmacoepidemiology . *N Engl J Med.* 2007;357(22):2219-2221. doi:10.1056/NEJMp0706892
28. Wang S V, Schneeweiss S, Gagne JJ, et al. Using Real-World Data to Extrapolate Evidence From Randomized Controlled Trials. *Clin Pharmacol Ther.* 2019;105(5):1156-1163. doi:10.1002/cpt.1210
29. Schneeweiss S. Real-World Evidence of Treatment Effects: The Useful and the Misleading. *Clin Pharmacol Ther.* 2019;106(1):43-44. doi:10.1002/cpt.1405
30. Gagne JJ, Rassen JA, Walker AM, Glynn RJ, Schneeweiss S. Active Safety Monitoring of New Medical Products Using Electronic Healthcare Data. *Epidemiology.* 2012;23(2):238-246. doi:10.1097/EDE.0b013e3182459d7d
31. Fralick M, Kesselheim AS, Avorn J, Schneeweiss S. Use of health care databases to support supplemental indications of approved medications. *JAMA Intern Med.* 2018;178(1):55-63. doi:10.1001/jamainternmed.2017.3919
32. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med.* 2020:1-10. doi:10.1056/nejmoa2006923
33. Mehra MR, Ruschitzka F, Patel AN. Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis (The Lancet, (S0140673620311806), (10.1016/S0140-6736(20)31180-6)). *Lancet.* 2020;395(10240):1820. doi:10.1016/S0140-6736(20)31324-6
34. Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621. *N Engl J Med.* 2020:2021225. doi:10.1056/nejmc2021225
35. Nayak RK, Avorn J, Kesselheim AS. Public sector financial support for late stage discovery of new drugs in the United States: Cohort study. *BMJ.* 2019;367:1-12. doi:10.1136/bmj.l5766
36. Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs. Hamel MB, ed. *N Engl J Med.* 2015;372(3):279-286. doi:10.1056/NEJMhle1409465
37. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med.* 2020:2327-2336. doi:10.1056/nejmoa2007016
38. Joffe S, Lynch HF. Federal Right-to-Try Legislation — Threatening the FDA's Public Health Mission. *N Engl J Med.* 2018;378(8):695-697. doi:10.1056/NEJMp1714054
39. Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HM, Ross JS. Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies. *N Engl J Med.* 2012;366(24):2284-2293. doi:10.1056/NEJMsa1200223
40. US Food and Drug Adminstration (FDA), Office of Counterterrorism and Emerging Threats (OCET). Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities#footnote1. Published 2017. Accessed March 28, 2020.
41. Birnkrant D, Cox E. The emergency use authorization of peramivir for treatment of 2009

H1N1 influenza. *N Engl J Med.* 2009;361(23):2204-2207. doi:10.1056/NEJMp0910479

42. Zhai MZ, Lye CT, Kesselheim AS. Need for Transparency and Reliable Evidence in Emergency Use Authorizations for Coronavirus Disease 2019 (COVID-19) Therapies. *JAMA Intern Med.* 2020;323(19):1899-1900. doi:10.1001/jamainternmed.2020.2402
43. Pavia AT. What did we learn from the emergency use authorization of peramivir in 2009? *Clin Infect Dis.* 2012;55(1):16-18. doi:10.1093/cid/cis365
44. Yu Y, Garg S, Yu PA, et al. Peramivir use for treatment of hospitalized patients with influenza a(H1N1)pdm09 under emergency use authorization, october 2009-june 2010. *Clin Infect Dis.* 2012;55(1):8-15. doi:10.1093/cid/cis352
45. Sorbello A, Jones SC, Carter W, et al. Emergency use authorization for intravenous peramivir: Evaluation of safety in the treatment of hospitalized patients infected with 2009 H1N1 influenza a virus. *Clin Infect Dis.* 2012;55(1):1-7. doi:10.1093/cid/cis351
46. Ison MG, Wolfe C, Boucher HW. Emergency Use Authorization of Remdesivir. *JAMA.* 2020;55(1):1-7. doi:10.1001/jama.2020.8863

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Chairman FOSTER. Thank you. And my apologies again for having skipped your testimony in the order. That's, I guess, the danger that occurs when I've read your testimony in advance and feel less need to hear it directly from you.

And so I guess I will repeat my question, which is largely directed at your testimony to say a little bit more about the differences in the way things are being done internationally versus in the United States and what lessons we might learn from that.

Dr. ROME. Thank you, yes, I am appreciative. So, the—your question is a good one. We have had two successes in this pandemic so far with dexamethasone and remdesivir. One was primarily driven out of the United States, but the other, dexamethasone came from funding from other countries. And I can say that most of the large clinical trials that are being conducted, especially the ones that were started very, very early in the pandemic and are likely to get us results in a timely fashion, were led by our peers in Europe and other countries. And definitely the United States should, in going forward in this pandemic and in future pandemics, lead those efforts and become a leader in the world for running these sorts of clinical trials.

Chairman FOSTER. Now, in the case of the drug that worked, the anti-inflammatory that worked in England, was that funded by the manufacturer? Because one of the things that worries me here is that if all—if the majority of our clinical trials are funded by manufacturers, you will naturally—they will prefer drugs for which they have an intellectual property or a manufacturing position in and that we may forgo equally promising drugs that are, for example, off patent or just become generic drugs. And is that handled differently in other countries than the United States or are essentially all trials worldwide funded by the manufacturer?

Dr. ROME. No, not all trials are funded by the manufacturer. And the trial out of Oxford was funded by the U.K. Government. Dexamethasone is a generic drug. There's very little skin in the game for any manufacturer to conduct a clinical trial, and that's likely to be true of many of these repurposed drugs, which may be older, off patent, generic drugs, which are widely available and great for patients but not necessarily a good investment from the perspective of a manufacturer.

But not only that, the clinical trial for remdesivir, which is still a patented drug owed by Gilead, the key clinical trial upon which we are using the drug and an EUA was based was funded by the U.S. Government, by the NIAID (National Institute of Allergy and Infectious Diseases), and so—and this is a case where Gilead should have been running the key clinical trials and instead ran a clinical trial testing two different doses of the medication against itself and leaving the key clinical trial to come to the U.S. Government. And they have a patent on that drug and can financially benefit from it when it—or if and when it gets FDA approved.

Chairman FOSTER. Thank you. Yes, Dr. Lurie, any comments on what's done internationally versus the United States and lessons we might learn?

Dr. LURIE. Well, I think what Dr. Rome said is spot on the money. Unfortunately, things have been to a certain extent delegated to the pharmaceutical industry and even to individual aca-

demic institutions in this country. What we really need is somebody to coordinate the whole thing. I know that the NIH would like to do that. I know that the British Government has done so very successfully, particularly in the Recovery Trial, but we need a stronger hand on the rudder, somebody to prioritize the drugs, figure out the ones that matter the most, and then do proper trials on them.

I guess I'd add it to what Dr. Rome said in the following way. It's tempting in the setting of a pandemic to say that we need to cut corners, but actually, the pandemic is almost the best place to stick with the usual game plan because there are so many patients, I'm sorry to say, and the disease makes you ill so quickly, I'm sorry to say, that there's more than enough statistical power for people to do the randomized controlled trials which we expect drug approval to be based upon.

So, let's stick with the methods that work. Let's not use the pandemic as some excuse for corner-cutting or for deregulation.

Chairman FOSTER. All right. So, yes, that's interesting. Do you think that there may be opportunities that we're overlooking for sort of lightweight outpatient clinical trials? You know, you can imagine to have a quick but scientifically valid look at hydroxychloroquine, for example, if you had any one of the—some fraction of the large number of people who have tested positive were immediately given the option of being screened and just on an outpatient basis given that we could've rapidly understood and, you know, with a lot of safety concern. Are there opportunities there we should think about?

Dr. LURIE. I think there are, but so far if you look at the totality of the research that's been done, most of it is based on the inpatient setting, and that makes a certain kind of sense. These are the sickest patients after all. They're the patients in whom you can demonstrate benefit most easily. So, I agree there's opportunity, but I don't mean that as a criticism of the research enterprise to date.

Chairman FOSTER. All right. And that exceeds my 5 minutes, and so I'd like to recognize Representative Lucas—Chairman Lucas for 5 minutes.

Mr. LUCAS. Thank you, Mr. Chairman.

Dr. Stevens, could you provide us with an example of a cutting-edge research capability unique to the Argonne National Lab and how it is helping researchers work forward toward repurposing existing drugs to treat COVID–19?

Dr. STEVENS. Well, the—probably the best example is the use of the advanced photon source to quickly within a few days, assuming we can get a good crystal, produce a new structure of a viral protein bound to a drug. This is critical to understand whether or not the target is in fact the target that the drug is working on to understand how it changes the structure of the protein, how it might interrupt its function, so that's a pretty unique capability. There's only a handful of places in the United States and the world that can do that and can do it quickly.

And after the pandemic became apparent and Argonne went into a lowered level of operation, we kept the advanced photon source

up, and we kept that team working on determining protein structures critical to the virus. That's a really good example.

Mr. LUCAS. Well, could you, along those lines, explain how Argonne National Lab is working collaboratively with other research entities toward identifying COVID–19 drug candidates?

Dr. STEVENS. So, we have a nine-lab consortium that includes Argonne, Oak Ridge, Berkeley, Brookhaven, Los Alamos, Livermore, Sandia National Laboratories, SLAC, and Pacific Northwest Labs, nine labs all working together. We are using large-scale computation to computationally screen drugs, billions of drugs—or billions of potential drugs. All the existing drugs and billions of molecules that can become potential drugs. The drugs that look interesting from a computational standpoint are immediately procured and turned over to experimentalists that can assay the drug to determine if it is a viable inhibitor of function.

And for things that succeed at that functional screen are forwarded to whole cell assays that can test full virus replication. Things that would succeed there would get passed on to animal models and then passed on for additional refinement and development. But I point out that it takes a large team to do this with virologists, physicians, medicinal chemists, computer scientists, and so on, and because of that large team—in fact, an important strategy is to consider repurposing existing drugs alongside new compounds. Existing drugs are of particular interest to clinicians due to them already being available.

Mr. LUCAS. As I mentioned earlier, my bill, H.R. 6599, focuses on collaboration among Federal agencies and aims to create a national strategy for any infectious disease outbreaks we face in the future, and certainly we will face those in the future again, as the Chairman alluded to. Are there any other collaborations that we're not thinking about that would help you, Dr. Stevens?

Dr. STEVENS. Well, we—early on, we established a collaboration between the DOE national labs, and the NIH, which has laboratory activities and research groups, so there's linkage. I think what's needed in the framework of your bill is a sustained, ongoing network of research collaborations that's consistently working on problems and is sharing data, sharing research, sharing assays, sharing information and would involve the DOE, it would involve the NIH, it probably would involve NSF resources in some cases, the DOD (Department of Defense), essentially all the players that are necessary for integrated public health in this country—some kind of ongoing collaboration around emerging threats.

Mr. LUCAS. One last question, Dr. Stevens. Is there anything Congress can do to help scientists and researchers like yourself do their jobs more efficiently during this pandemic and bring us one step closer to ultimately a cure?

Dr. STEVENS. I believe that the current activity is exactly what's needed. The funding—the ongoing funding support for these new efforts is of course critical, extend that longer. We're not out of this pandemic yet. I believe the interagency coordination process is working quite well. I believe that the institutions have put together structures to support this. Within the Department of Energy, for example, they created the National Virtual Biotechnology Lab coordination process across all the national labs in the United States

to drive them toward a coherent COVID–19 strategy, so I believe that's working. So, continued support for that level of activity is what I recommend.

Mr. LUCAS. Thank you, Doctor. Thank you, Mr. Chairman. I yield back.

Chairman FOSTER. Thank you. And I will now recognize Representative Bonamici for 5 minutes.

Ms. BONAMICI. Thank you, Mr. Chairman. Can you hear me?

Chairman FOSTER. Yes.

Ms. BONAMICI. Terrific. Well, thank you to Chair Foster and Ranking Member Lucas and really for—to our witnesses today. Thank you for your expertise.

We know that COVID–19 is disproportionately affecting black, Latinx, indigenous, and other people of color and that they are contracting the disease and dying at alarming rates. And as researchers develop studies and carry out trials, the Administration and Congress can and must address these disparities and do all we can to encourage or require research that's deliberately inclusive of all demographics and effectively addresses these inequitable outcomes.

Recruiting patients to participate in research we understand can be challenging even under ideal settings, but trials can fail if there's a lack of patient enrollment. There are valid reasons why a patient invited to take place in a study may not trust medical researchers or feel comfortable participating. And even once a willing participant is identified, there can be barriers to their inclusion.

A recent *Politico* article talked about physicians who were conducting NIH-funded clinical trials for remdesivir at sites in Boston, New York, and Atlanta. They faced language barriers in recruiting patients with limited English proficiency. They didn't have consent forms in Spanish. They had to work with translators by phone to explain the study and get consent and took extra hours per patient.

So, I know, Dr. Lurie, you mentioned this. Do the witnesses all agree that it's important to have diverse representation in studies and trials? Do you all acknowledge that that's important?

Dr. LURIE. Well, if I may go, I most certainly do. I've not seen specific information about recruitment and how it might vary by ethnicity so far in this pandemic, but I do know that this is not an equal-opportunity virus. At all stages of this disease, African Americans and other people of color are at a distinct disadvantage. They're more likely to be exposed to the virus in that they're more likely to be living in crowded living conditions, more likely to be working in meatpacking plants, more likely to be in prison, more likely to be healthcare workers at the front lines of exposure to the virus.

After that, they very often have difficulty gaining access to treatment in part because of lack of health insurance, and then within the hospital, you know, the outcomes have not been equal across ethnic groups perhaps because of significant underlying health care—health conditions as well.

So, all the way across——

Ms. BONAMICI. I appreciate that. I'm going to ask—I don't mean to interrupt, Dr. Lurie, but I'm also going to ask you and Dr. Finigan, are there strategies to get diverse representation in testing and trials? And, if not, what could not only the government but

what can the medical community do? Do you have suggestions on how to build trust in the communities that may have been historically excluded from government-funded research? I want to get your thoughts and also Dr. Finigan.

Dr. LURIE. Well, Dr. Finigan, go ahead.

Dr. FINIGAN. Thank you. So, first off, you're correct. So, I would—I have seen firsthand in the COVID–19 pandemic where we—there have been examples of people who were not recruited adequately or were not recruited because there was a language barrier, there was not an appropriate consent form. That was particularly challenging for people who only spoke Spanish. One important thing to note is that there's often—there's always a time window in which you can recruit somebody, so, you—typically, you can't recruit somebody into a study in an unlimited time window, that you may have to do it within, let's say, 24 or 48 hours of them being positive, and so there's a little bit of a race against the clock in this. And so those kinds of barriers really can have significant meaning. I think those things need to be taken into account ahead of time.

It is relatively common that African Americans, Latinos, nonwhites are sort of underrepresented in studies, and so being ready for that kind of thing ahead of time to make sure they can get adequately enrolled, all the resources are available to them, those things are critical. I know of studies where they got those kinds of resources, those consent forms, but it happened weeks into the trial, and so you lost time, you lost patients.

And the other critical piece there that I think you're also getting at is that's a lost opportunity for that person to be in a trial. Our goal is to give every patient the opportunity to enroll in a trial if they want to. And if you can't enroll them because there's not an adequate consent form, let's say, that's a missed opportunity for that patient, and they may lose the chance of being in a trial, let's say, on remdesivir where there's a potential benefit.

Ms. BONAMICI. I appreciate that. And there was just an article this morning in Axios Health Newsletter that there's all this—now there's talk this week about this steroid that's been hailed as a breakthrough treatment, but there's also evidence, according to the Chair of Pharmacology at Johns Hopkins University School of Medicine that African Americans may respond differently to this type of steroid. So, it's so critical that we address this issue because, as we know, COVID–19 doesn't discriminate based on somebody's race. I mean, it's disproportionately affecting people of color.

And real quickly, Dr. Finigan, we know that repurposing existing drugs is an attractive option because medications have already gone through testing. Can you tell us more about how preclinical testing in clinical trial phases can be safely accelerated if the drug has already been approved for another use?

Dr. FINIGAN. So, there are—so there are different ways this can be done, but I think the key is to have sort of integrated networks so you can hit all the phases at once. So, as has been described, there are things you can do, Insilico, in a computer where you can try to rationally identify drugs. So, for example, I was a part of a study where one of our investigators built essentially a Google program where you could put in drugs and then put in the kind of

drug you wanted or the kind of protein you wanted to target, and then this computer program would sort of spit out the drug that you wanted, and then you could marry that to an assay that you could do in a lab where you might have, let's say, 500 little wells, and you could test different drugs in each one of those wells. And so being able to marry those different things together and being able to do that and then rapidly move that into an animal model, those things are important, to have that whole spectrum represented. Whether or not that requires one institution or multiple institutions is important.

And I think, as was said earlier, having these assays sort of ready to go is important, and so thinking about what these might be, they often have to do with toxicity, whether or not they kill cells or something like that, those are the things that need to be thought about ahead of time so they can be ready to go.

Chairman FOSTER. OK. So, I'm afraid I have to——

Ms. BONAMICI. OK. My—yes, my time is expired. I yield back, Mr. Chairman, thank you.

Chairman FOSTER. That's all right. And we'll have a little bit of forbearance with Representatives who are coming in on the telephone because they can't see the timer.

And we'll now recognize Representative Biggs for 5 minutes.

Mr. BIGGS. Thank you, Mr. Chairman, and thanks, Ranking Member Lucas, and thank you to each Member of the panel. This has been very interesting.

And as we're trying to develop vaccine or cures for the COVID, I see we're moving fairly rapidly. It looks like we're moving rapidly. And I appreciate Dr. Lurie talking through this, maintaining some standards and normalcy.

But I guess my question that I want to ask here is, as we go through this and we accelerate these processes, can you address, and I'll just open it up to whoever wants to answer this. How can we maintain scientific rigor while we're accelerating the development of vaccines and curatives? And each one of you have nibbled around the edges here, but I'm wondering if there's any way that you see that we can maintain that scientific rigor that's so necessary if we're going to really get a handle on this?

Dr. LURIE. Well, you know, I think the playbook is clear. The playbook is the playbook that we've had for decades, the playbook that has produced effective therapy through following that very playbook, through keeping to strong standards. So, all I think we really need to do is to coordinate better, obviously speed things up the way researchers collectively have decided to do by turning their attention to this. And if we keep our standards up, I like to think that ultimately we'll have the products that we need.

Mr. BIGGS. Well, and so that gets me to Dr. Rome, who I think mentioned something I'm in total agreement with if you'd maybe expand on that. You said in EUAs one of the things that we need to do is be more transparent. And so, Dr. Rome, if you would just address that, how we do that and how can we best be more transparent?

Dr. ROME. Yes, thank you. I totally agree. Transparency is key with EUAs. We had two examples of EUAs or emergency use authorizations so far during this pandemic, so hydroxychloroquine

and chloroquine was the first one. That was based on very little evidence. But when the EUA came out, it wasn't clear what evidence the FDA had considered, and it sort of—only later did we sort of learn a little bit about what they—what was going through the minds of the folks at the FDA.

With remdesivir, we had a top-line result published by the clinical trial, but we—not until 3 weeks later did we have the full data that was released in the *New England Journal of Medicine*. And during those 3 weeks the drug was already being shipped out to hospitals and humans, and we didn't know necessarily how to best target the drug toward particular patients or if there was—and we had a limited supply.

So, absolutely, transparency is key. The FDA should make decisions in a consistent way that meet the standard. The standard for any EUA is that it is reasonable to believe, based on the totality of evidence, that the drug is likely to be effective. So, that reasonable-to-believe standard needs to be enforced. When new data comes out, we need to reassess. And we need the—whatever data that the FDA is using to make those decisions should be public at the same moment that the EUA letter is issued.

Mr. BIGGS. Great. Thank you. And I'm just going to go to Dr. Stevens. Dr. Stevens, you mentioned that although repurposing existing drugs may be a fast route to possible treatments, it's highly likely that we're going to still need purpose-built drugs for treating COVID–19. Can you expand on how the work that you're doing at Argonne be leveraged by pharmaceutical companies to help develop purpose-built drugs specifically?

Dr. STEVENS. Yes. So, what the team is doing is we are trying to produce a set of qualified leads. That would be compounds that show some promise in the computational work, they show some promise in initial functional assays and initial whole cell assays but are not fully refined as drugs. These would be compounds that we would essentially handover to the pharmaceutical industry and say here's all the data that we've computed and that we've measured on these compounds and let them take it from there.

And this—that kind of handoff has been discussed between the labs and pharma, and it's the kind of thing that pharma is very interested in because you think of the—the drug and all the processes is a giant funnel, and at the top of the funnel you've got billions of possible molecules out of the—out of 10 to the 60th possible drug molecules, we know of a few billion of them that we've thought about in some sense, and we have to narrow that down to handfuls, you know, 10's or 20's of compounds the pharmaceutical industry can take and do more advanced studies on, can refine and improve the molecules, improve their safety, improve their effectiveness, improve the therapeutic window.

And so what we're doing in the public sector is essentially that big top part of the funnel and reducing it down in a very public way, in a very open way, to set of priorities that they can then take and invest private money into drugs. That's the strategy.

Mr. BIGGS. Right. Thank you. And with that, Mr. Chairman, I'll yield back.

Chairman FOSTER. Thank you. And I will now recognize Mr. Beyer for 5 minutes.

Mr. BEYER. Thank you, Mr. Chairman, and thanks, all of you, for being with us.

Let me begin with Dr. Rome. One of the things in your testimony you said it's imperative that we establish a clinical trial network. Does one not already exist, and isn't that part of the function of NIH to have established that over the years?

Dr. ROME. Thank you for the question. Yes, so, certainly, we have small networks of clinical trials, and I think that Dr. Finigan could probably speak to this more as a trialist himself, but I would say that the NIH does in fact do direct research itself in some cases, as was the case in remdesivir. But in other cases it will outsource to academics. And, as was already mentioned, when a study is done at multiple sites, there's a lot of regulatory things that need to happen. You need to assure safety of the clinical trial through institutional review boards, and that can take a long time.

And so by—what I think the—where I think the efforts need to be is, you know, clinical trialists and scientists are ready to go and want to act. What needs to be cut down on are the things that are super important like maintaining patient safety, but the time to do those things and the time to correlate across different sites can definitely be cut down on by investing further in those infrastructures.

Mr. BEYER. The vision has to be that there is an existing national network of clinical sites, say, 50, 100, 300, that in a future crisis, click, you turn it on.

So, to Dr. Finigan, you mentioned that at National Jewish Health you're working on delineating the structure of the protein. Why would an individual hospital do that rather than the national labs that have all the—you know, the big computing machines, the neutron devices and the light devices?

Dr. FINIGAN. You know, I mean, it has to—so it has to do with a couple things. No. 1, ability and interest. We have people who have that ability and can do it. And, as I said, everything is sort of reoriented toward COVID–19, so everybody in the hospital dropped what they were doing and started to do new things directed toward COVID–19. So, people who had that ability here worked on that.

I think it also speaks to a little bit of a lack of coordination of how this would be attacked from the beginning, and so from the beginning there was not a sort of—at least not a publicly announced kind of strategy that was clear to everybody in terms of how things were going to happen, how things were going to get laid out from sort of basic science, understanding some of those basic facts to driving it into clinical trials, and that creates a fair amount of duplication.

And an example of that, just to answer the question you brought up earlier, there are clinical networks that have existed, and there are lots of them that still exist. It's just that it took several months to utilize those for COVID–19. They sat not being used for COVID–19 trials for a period of time, and now they're starting to get used. And so it may not be creating a new network. It just means understanding that these things exist and you have a strategy ready to go that you're going to use.

Mr. BEYER. Great, thank you. Thank you. Dr. Stevens, I was fascinated by the notion that the COVID—you know, the RNA translates into 30 specific proteins. You understand the structure, how they're folded, that 10 to 20 of them are what creates this issue. And you talk about purpose-built. Is it—are you thinking or is it possible to think—and I think mathematically with your supercomputers about how to tear apart one of those 20 proteins?

Dr. STEVENS. Well, we're building both physics-based models and AI models to essentially design—custom design inhibitor molecules for each of those proteins using the power of supercomputing. I mean, that's what the community that can do this type of biophysical modeling and AI is working on. There are many groups that are collaborating on this task, and I believe in the near future—I can't say exactly how long this will take—we will have new compounds that are the result of this process that will go into the experimental screening pipelines.

Mr. BEYER. But do you have to disrupt more than one of those 20 proteins to make a——

Dr. STEVENS. Yes, you have to. If you look at state-of-the-art antiviral therapies, often they're a cocktail of drugs, and so we think the best strategy is probably a multiple therapeutic mix that would go after multiple targets, maybe a target that would help in blocking viral entry, one that might block replication, one that might block some host process that is a problem, and so forth. And so you would probably end up at the end of the day with a mixture of compounds in a future drug—or future drug treatment.

I think it's really important, though, to say that to develop the kind of drugs that we're imagining will take a long time. If you think about in the case of HIV, it took many, many years before there were effective HIV therapies, over a decade, and while we're moving faster, and we have better tools, this is a very hard problem. And while the scientific community has been working the last few months in a kind of crisis mode on this, they can't work in crisis mode for many years, and so we have to put institutional structures around this to get it done.

Mr. BEYER. Thank you very much. And I yield back, Mr. Chairman.

Chairman FOSTER. Thank you. I'll recognize Representative Wexton for 5 minutes. Mute. Whoops, microphone. Mute. You're muted.

Ms. WEXTON. Shame on me. Hi. Thank you, Mr. Chairman, for yielding and for not charging me my 5 minutes quite yet. And to the panelists for joining us today, this is a really fascinating discussion, and I'm glad to be here for it.

You know, the controversy surrounding the FDA's EUA for hydroxychloroquine has caused a lot of people to question the scientific integrity of FDA's process, and so the policymaking especially during this pandemic. Dr. Lurie and Dr. Rome, could you please give us your general assessment of the rigor of FDA policymaking and public communications regarding the repurposing of therapeutic drugs during this pandemic and then what needs to be done better, if anything?

Dr. LURIE. Well, I certainly agree that it has been a disappointment, and I don't think it's because of the career officials in FDA,

who I believe are completely committed to scientific integrity and proper regulatory procedures in this pandemic. But I do think that people have turned out to be susceptible to political pressure.

The hydroxychloroquine example is frankly an embarrassment. The standard for approving the EUA was considerably below what it was in previous EUAs, and I say this based on talking to people who granted EUAs in previous Administrations. And so, in the end, that turned out to be a black eye for the agency.

Another embarrassment I think has turned out to be antibody tests where for a while the agency allowed these products to come on the market without even an EUA. And then that turned out to be a disaster when it turned out that they were plagued by false positives, so now they have an EUA.

What I hope is that from the combination of those two experiences we'll get a proper use of the EUA process, which I think we are now seeing for remdesivir, and I sincerely believe and hope that my former colleagues at FDA will be able to stand up to the political pressure, because it is certainly searing.

Ms. WEXTON. And Dr. Rome, how about you?

Dr. ROME. Yes, thank you for the question. I think what you're getting at is actually an issue that has come up again and again, which is sort of the standards of evidence sort of required for any drug approval even before COVID–19, which traditionally were statutorily supposed to be based on sort of substantial evidence, so it means that traditionally that meant two clinical trials, two large randomized clinical trials to make sure that even if one trial got the answer wrong, that we wouldn't get it wrong twice. And that has changed over time.

There are many drugs now that are expedited through the FDA process, and that's something that needs to be considered. And that's sort of the background for when—you know, when COVID–19 came, we've already experienced the fact that 80-plus percent of drugs are approved through some expedited pathway may be based on more limited evidence than that traditional two clinical trials. So, during COVID–19, we've relied, you know, on the EUA to sort of cutoff the FDA approval process and act before the FDA sort of carefully considers all the evidence.

It makes total sense, and certainly time is of the essence, but to your point, we actually have very little experience using EUAs in—for drugs. It was done during a swine flu pandemic of 2009, 2010. There, a drug was issued an EUA, and the—but data that later came out from the clinical trials showed that the drug was not actually effective for the type of patients the EUA was issued for.

Now, we have hydroxychloroquine and remdesivir, so we've maybe hit one out of three potentially that we don't know the full story on remdesivir, but certainly this is the time for Congress to take a look at the way the EUAs have been utilized and tune up the regulations on the FDA to make sure it's done appropriately in the context of the speed that's needed.

Ms. WEXTON. So, in this final minute I guess my question is also there's going to be a lot of financial incentives for various firms to get their drugs through this EUA process and get them approved. What—how does the FDA assess and eliminate conflicts of interest

in its drug approval process, make sure that there's no conflicts in the decisionmaking process?

Dr. LURIE. Well, I—quite frankly, the process is infected with conflict of interest, and there's not very much that can be done about it in the following sense. We accept the idea that drug trials, trials of diagnostics and vaccines, are conducted in general by the manufacturers themselves, and so it's a given that there will be that kind of conflict of interest in that the companies will come in with an interest in depicting the data in the way that best suits them.

But that's where the FDA comes in. That's where the FDA's review of the actual data itself, which no other country in the world claims to do, that's where that kind of review, that kind of insulating of the reviewers from the manufacturers is so important. And that's the way it's managed. But it's a given that most of the time the studies will be done by the manufacturers themselves.

Ms. WEXTON. Thank you very much. I see my time has expired, and I will yield back.

Chairman FOSTER. Well, thank you. And I will now recognize Representative Perlmutter to unmute and——

Mr. PERLMUTTER. Thanks, Mr. Chair. And to the panelists, thank you all for your testimony. I've been watching you all listen and watch each other, and it's been interesting.

So, the first question I have—and, Dr. Finigan, you brought up a couple networks, and you say there are networks in place, but they really didn't get activated promptly. So, you talked about ACTIV and you talked about PETAL I guess, sort of the acronyms for these things. And to everybody but start with you, Dr. Finigan, a pandemic comes, we see this thing starting to roll, how is there—is there some lead agency, is it CDC, is it NIH, is it BARDA, is it—who is it that says to these networks, OK, everybody's got to jump to whether it's hospitals or the laboratories or who says "get going?"

Dr. FINIGAN. So, I think to a certain degree the exact agency that does it doesn't matter. I think it just needs to be understood out of time. And so whether or not it is the NIH or BARDA, it—you know, or another agency, I don't think really matters. It's just a function of thinking ahead of time and knowing ahead of time that these networks exist and that you want to put them into action and especially in a situation like this where you actually have some lead time. So, we knew about this pandemic for some time, and we could have been planning it, and so it doesn't necessarily matter that it's the CDC or a different agency. Whichever agency, let's say, funds that network or if you need to bring in more than one network and you might need to have cross agency, those things just need to be thought of ahead of time.

Other aspects like how you would do consenting for patients and those things also should be thought of ahead of time so that that can be streamlined as quickly as possible for when you need to utilize those networks.

Mr. PERLMUTTER. So, Dr. Stevens, when were the labs sort of kicked into gear on this thing?

Dr. STEVENS. The labs started to self-organize around the 1st of March ahead of the official proclamations. We have a bit of internal

flexibility at the labs and we used that flexibility to get started. That's why the labs exist, to do large-scale science, interdisciplinary, and so—and we're used to taking initiatives on our own, taking our own initiatives, so the labs started talking to each other, we started arranging computer time, we started pulling together teams actually long before the pandemic was declared. And DOE headquarters was very supportive that we were already moving.

And so I think the community—I think the others would—panelists would agree. The community saw this coming and started to do things that they could do within the realm of their degrees of freedom of action, and the agencies then came up to speed to start resourcing things. So, I think, you know, it all sort of happened in parallel.

Mr. PERLMUTTER. So, to all of you, from our—so our Science Committee we have a little bit of jurisdiction with respect to hospitals but not a lot, but we do have definitely jurisdiction over the laboratories. So, is there any connection in these networks that you talked about, Dr. Finigan, or you talked about the nine labs that you're collaborating with, Dr. Stevens? Is there any connection between sort of these hospital networks and our laboratories? Are you guys talking to each other?

Dr. STEVENS. Not so much. The Department of Energy typically doesn't get involved in clinical research. Our laboratory doesn't have ongoing internal projects related to clinical work. This is largely due to the distinctions between the different agencies that fund that work. We do have a lot of collaborators in universities, and so the way in which we—and I personally have a joint appointment at the University of Chicago where I have colleagues in clinical trials and I have funding from NIH and connections to clinical work via my university appointment and from talking to those people so, personally, we have contacts. But, institutionally, the Department of Energy, typically, the DOE laboratories that they support aren't involved in clinical work.

Mr. PERLMUTTER. All right. Well, let me turn to Dr. Rome for my last 45 seconds. So, at Harvard—so National Jewish collaborates with lots of hospitals, the University of Colorado, a bunch of other stuff. Harvard obviously collaborates with everything around the world. When did your medical school and when did you sort of—or how—get engaged in this thing, I mean, the minute we heard about it from China or how did that go?

Dr. ROME. I agree with what's been said that the scientific community acted early, but acting early involves having information, and I think the information comes from the top in this case. The information out of China was challenging, I think, for medical professionals to understand, and so by the time in March that people started to gear up here, that might have been unfortunately pushed earlier had the Administration and everyone else in the government sort of set the ball moving and pushed for action earlier on.

Mr. PERLMUTTER. And I guess I was remiss to say Dr. Finigan helped me on a telephone town hall where we had 10,000 people on the line, and so I just wanted to mention that and thank all of you for your testimony today. I really appreciate it.

Chairman FOSTER. Well, thank you all. At this point I guess there's probably enough Member interest for another round of questioning for those Members who wish, and so we can quickly—all right. Mr. Perlmutter and Beyer. OK. So, this may be a brief round of questions here, but I would like to follow up on a couple of points.

The—Dr. Finigan, you sort of mentioned the idea, the concept that there—instead of having to replicate the approval of the remdesivir trial at 60 different locations, that there could be some single point of approval. And are you—is it realistic to expect that individual institutions will buy into that mechanism, that they'll be willing to outsource the approval of a clinical trial that may or may not, you know, be safe, which is one of their concerns?

Dr. FINIGAN. So, the answer is no, they're not going to give it up, but I think there's things you can do ahead of time to make it go much faster. So, what happens with a trial like the remdesivir trial or other trials that we have going on is an industry sponsor in these instances reaches out to us, asks us if we want to be a part of it. We say yes, and then there—at that point you begin the back-and-forth of we get the protocol, we read it, it goes through our process, we have to approve it and make sure it's safe, we have to discuss the budget, we need to make sure we have to do it. While we're—they're doing that with us, they're doing that individually at all the different sites. If we spend, let's say, 3 weeks working on it and then decide we can't do it, that's wasted time for everybody.

So, if this—so if you have a network like, let's say, the PETAL network that I mentioned, this exists already in place. A lot of that work has been taken care of already, and so a lot of that immediate work and legwork in terms of getting things approved and contracting and budgeting, that stuff might be taken care of. And so you can imagine a situation where a drug company might say I have a drug, I think it's promising, I want to use this federally funded network and maybe there's some mechanism by which they have to pay in to use that to help keep that funded but allows them to very rapidly get their drug out there and not have to go through the process every time.

Chairman FOSTER. All right. And so, yes, you touched on the issue of getting the commercial incentives right, because that must be very delicate in this because, you know, obviously if a drug company can get the Federal taxpayer to pay for a clinical trial for a drug that they'll eventually make money on, you know, say this is something which is a currently unapproved use, you'd think that there ought to be a mechanism in place somehow to have the drug—the Federal taxpayer, you know, have some benefit from the fact that they paid for this trial.

And are there countries anywhere that have a different model that might be more effective for dealing with the—you know, the commercial interest to fund trials, or do they just fully federalize it and there's a big pot of money that—and a group of scientists who decide what is the most scientifically promising and allocate some fraction of the clinical trials that way?

Dr. FINIGAN. So, I can't speak to what happens very knowledgeably in other countries. I'll let other people address that if they know that. What I will say briefly is that there are some examples

of—I don't know if it's quite public-private partnerships but, for example, in cystic fibrosis, the Cystic Fibrosis Foundation, which really sort of regulates a lot of the trials that happen in cystic fibrosis in kids and adults, partnered with an industry sponsor on new drugs so that they could rapidly get those drugs sort of tested, and then those were successful and approved, and so the drug company and the Cystic Fibrosis Foundation both benefited from that. And I think that's an example that could be replicated in other instances. And I'll let others talk about other countries.

Chairman FOSTER. Dr. Rome, any comments?

Dr. ROME. Yes, I guess I would say that I don't know of another country sort of to your question of sort of how that balance is made other than other countries do a much better job negotiating for value-based prices of drugs so that we do not sort of double pay, paying sort of through the roof for clinical research to develop the drug and then secondarily for high prices, so that's one comment.

The other is that not just in COVID–19, again, I mentioned the example of remdesivir, which is exactly what you said. A government is funding the late stage sort of clinical trial development. That occurs in one in four drugs that have been developed over the last decade where the Federal Government is involved late in the development of a drug. And almost every drug has some sort of Federal involvement in the early stages of development, so this is absolutely a problem. It's going to be highlighted in COVID–19, and it's going to affect how the drugs are able to be accessed by patients once we have to—you know, once patients and insurance companies have to pay for them, so it's definitely something that needs to be addressed.

Chairman FOSTER. Well, thank you. And I think one of the most potentially tragic outcomes is that promising drugs just won't get looked into that should if you don't set this up right. All right.

And at this point I'm happy to recognize Chairman Lucas for 5 minutes of additional questions.

Mr. LUCAS. Mr. Chairman, I will yield back but simply note our constituents out in the countryside are frantically looking for ways to protect themselves from this or cures to address it. I'd like to think that all the discussion here today about the challenges we face to this point, still the underlying issue is we're making progress, diligently working to address the needs of our constituents, and that they should have faith in the institutions both inside and outside the Federal Government that are working together, healthcare industry included, to try and address their needs, needs that are brought on through issues by no fault of their own, just the world we live in at this time.

And with that, Mr. Chairman, I yield back.

Chairman FOSTER. Thank you. And I'll now recognize Representative Beyer for 5 minutes.

Mr. BEYER. Thank you, Mr. Chairman, very much.

Dr. Stevens, in your testimony you talked about us paying attention in the long term to emerging pathogens. How do you define emerging pathogens? Does someone have to get sick before we do it? And given the billions of different viruses that are out there, what constitutes an emerging one?

Dr. STEVENS. Well, it's—there are several definitions, but the one that I think most people would agree with, it's pathogens that are relatively new to science, so these could be pathogens, zoonotic pathogens that are endemic in wild animals, maybe in places people don't normally live, and as humans, human development, and economic development pushes large numbers of people closer to these previously wild areas, there's lots of opportunity for contact with these animal species, and new pathogens can emerge that way. That's the primary mechanism.

If you think over the last couple of decades, the viral pathogens, Ebola, Zika, SARS, COVID–2—SARS-CoV–2, these have all emerged from animal reservoirs, and so my recommendation is that we mount a scientifically based international program to surveille wild populations, understand their microbiomes, the natural viruses that coexist with them, and study them. We have the technology for doing that. We could easily sequence these things. We can produce the structures. We can get ahead of the curve. We can understand the reservoirs much better than we do currently, and that would leave us more time to be ready for the next one.

Mr. BEYER. Thank you. You also mentioned that there are 10 million molecules available for experimental validation. Well, you can't—are you—and you talked about the windowing, the funneling.

Dr. STEVENS. That's right.

Mr. BEYER. Is the first funnel going to be a mathematical one, the physical one rather than experimental——

Dr. STEVENS. Well, the top of the funnel occurs in some theoretical sense as every molecule that's possibly drug like is about 10 to the 60th. The drug companies and the academic community have an understanding of maybe 4 to 5 billion molecules. Of that, maybe 10 million are something I can get my hands on in a couple of weeks. Of course, synthetic chemists can make new things roughly in that timeframe as well, so it would be conceivable to create ahead of time panels, that is, collections of molecules that are ready but essentially standing by in the freezers.

And if you have an emerging outbreak and you develop assays quickly, you could screen a very large set of molecules in a few months and have a lot of possible leads to chase down. And combining that with computation would create a much better situation in terms of future therapeutic development, and that's something I think the community would be very excited to work towards.

Mr. BEYER. Excellent. Thank you. And it is amazing trying to get your arms around 100 million molecules.

One last question. Dr. Rome, your fourth point was making improvements to FDA's EUA process, and you talked about the bullets, clarifying and standardizing transparency, equitable distribution, and then patient outcome data. Is this something that should be done regulatorily or is this a perfect piece of legislation for the House Science Committee?

Dr. ROME. So, the FDA has the ability to do some of these things but has not done so. They have the ability to collect information about the drugs, but they're not required to and—other than adverse event or safety reporting of sort of major events like deaths that occur from the drug, so that has happened, but further data

has not been required as part of the EUAs. The FDA has broad authority to write into the EUA sort of what it wants in terms of requirements, but certainly those requirements—you know, that sort of broad authority could be better regulated by Congress by sort of more directing and saying when you issue an EUA, these are the things that we think are necessary.

And we've learned a great deal about what would be helpful. I would say, again, more transparency at the outset so that physicians who are using the drugs from an EUA have access to data, you know, not just the data that's, you know, on the internet but actually like the raw data, the published studies.

Mr. BEYER. And you wouldn't think that we were guilty of micromanagement if we led that?

Dr. ROME. I mean, I think that these things need to happen, and so I think if Congress wants to step up and say that for all future EUAs that these are some tweaks that we think are necessary, I think that's reasonable. I would say the EUA is not just to drugs. The EUA applies to diagnostics, testing equipment that has been mentioned before, ventilators, other things. So, again, drugs are a minority of cases over the history of the EUA that have been—where it's been used, so we only have really three examples, two of which, you know, are for this pandemic alone. So, we are—you know, I do think it's time to reevaluate how that was used and decide if change—small changes, legislative changes need to be made.

Mr. BEYER. All right. Thank you very much. Mr. Chairman, I yield back.

Chairman FOSTER. Thank you. And I'll now recognize Representative Perlmutter for 5 minutes.

Mr. PERLMUTTER. Just one question, and start with you, Dr. Lurie. Anybody can jump in. The serologic tests, the antibody tests I guess, there are a whole bunch of them. Some have been approved, I guess, and some have not been approved. So, going to the diagnostics that you were talking about, Dr. Rome, did we do this right or not or is there now sort of doubt about these tests and their validity? Dr. Lurie?

Dr. LURIE. Well, in referring to the antibody tests specifically, I don't think that has been well-handled by FDA. I think that, feeling the pressure to press ahead, they gave the antibody tests a free pass to begin with, not even requiring an EUA for them. And it didn't take long for evidence to mount that, particularly in low-prevalence populations, certain of these tests could actually produce more false positives than true positives. And I think that first the agency took a look at what they'd done and then they slapped an EUA upon them giving the companies 10 days to comply. I don't know how many of them have met the EUA requirements at this point, but I expect that certain of those products will just disappear because they couldn't meet the standards.

So, again, what I'm sorry to say has happened is that the FDA has been—you know, they're kind of flip-flopping or, if you like, course-correcting, you know, to try and get this exactly right. They've made some mistakes. Hopefully, it will be better going forward.

Mr. PERLMUTTER. OK. Thank you. I don't know if anybody else has any comments. I just want to thank the panel, and I'm happy to yield back to you, Mr. Chairman.

Chairman FOSTER. Well, thank you. And I—you know, I have to say that I was a little bit surprised when the antibody tests came out so flawed, that there was no one responsible for making—for—in the government for establishing a test panel that you run every one of the proposed tests against just blood samples of positive and negative people that would be just prepared and at least given to every manufacturer to test against and report their results. And, you know, that seems like the sort of infrastructure that should exist somewhere in the future when this sort of thing happens.

And I was also fascinated by Representative Beyer's suggestion of potential legislation coming out of this, that there may be something sensible that could be done there. And, let's see, I can—now can—have about one remaining minute of Representative Perlmutter's time, so I'd just like—Dr. Stevens, how leaky is the funnel? How often do you see a drug that works wonderfully in practice and not at all in theory?

Dr. STEVENS. Well, it usually means our theory is wrong, so we have to go back and fix the theory if that happens. The funnel is pretty leaky in the sense that things fall out that we have to filter out because we're using approximate rules often to do this. But, you know, most of what we look at doesn't work. I mean, that's the reality of drug development. Most compounds don't work. And so it is a needle-in-a-haystack type of problem, and occasionally, you will find drugs that defy our, you know, initial view, but those usually don't come from the computational process because we filter those out. They would come through physical screens and natural products, for example, and then you have to go back and rethink them. So, you need combinations of both. This can't all be computationally driven. As I mentioned before, large chemical libraries that would be screened in public I think is another resource that we need as infrastructure.

Chairman FOSTER. All right. Well, anyway, I just want to thank all of our witnesses at this point before bringing the hearing to a close. It's very important. And keep thinking, as you're doing your daytime job here, what changes you'd like to see in place for the next pandemic because I think that's going to be a big part of our job is to try to preserve the attention span of Congress so that we're better prepared.

I guess someone smart once said you go to war with the army you have, and next time—next pandemic I'd like a slightly better army. And just thank you all for being part of the army that we have.

So, the record here will be open—remain open for 2 weeks for additional statements from Members for any additional questions that the Committee may ask the witnesses, and the witnesses are now excused, and the hearing is adjourned.

[Whereupon, at 3:04 p.m., the Subcommittee was adjourned.]

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