DISCUSSION PAPER

Health Product Manufacturers and Innovators COVID-19 Impact Assessment: Lessons Learned and Compelling Needs

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January 18, 2022

About the NAM series on Emerging Stronger After COVID-19: Priorities for Health System Transformation
This discussion paper is part of the National Academy of Medicine's Emerging Stronger After COVID-19: Priorities for Health System Transformation initiative, which commissioned papers from experts on how 9 key sectors of the health, health care, and biomedical science fields responded to and can be transformed in the wake of the COVID-19 pandemic. The views presented in this discussion paper and others in the series are those of the authors and do not represent formal consensus positions of the NAM, the National Academies of Sciences, Engineering, and Medicine, or the authors' organizations.
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ABSTRACT | *United States health care spending consumes nearly a fifth of the GDP [1]. While, in many respects, the U.S. health care system is enviable and highly innovative, it is also characterized by elements of ineffectiveness, inefficiency, and inequity. These aspects, resulting from pre-existing vulnerabilities within the system and interactions between the various stakeholders, were acutely highlighted by the COVID-19 pandemic. As health product manufacturers and innovators (HPMI) took steps to mitigate the immediate crisis and simultaneously begin to develop a longer-term sustainable solution, six common themes arose as areas for transformational change:*

1. *support for science,*
2. *data sharing,*
3. *supply chain resiliency, stockpiling, and surge capacity,*
4. *regulatory and reimbursement clarity and flexibility,*
5. *public- and private-sector coordination and communication, and*
6. *minimizing substandard care offerings.*

Within these categories, the authors of this paper suggest policy priorities to increase the effectiveness, efficiency, and equity of the HPMI sector and writ large across the U.S. health care system. These priorities call for increased scientific funding to diversify the pipeline for research and development, strengthening the nation's public health infrastructure, building and maintaining "ever warm" manufacturing capacity and related stockpiles, instituting efficient and effective

regulatory and reimbursement frameworks that promote innovation and creativity, devising structures and processes that enable more efficient collaboration and more effective communication to the public, and implementing rewards that incentivize desired behaviors among stakeholders. This assessment draws from the collective experience of the authors to provide a perspective for the diagnostics, hospital supplies and equipment, medical devices, therapeutics, and vaccines segments.

While the authors of this paper agree on a common set of key policies, sub-sector specific nuances are important to consider when putting any action priority into effect. With thoughtful implementation, these policies will enable a quicker, more robust response to future pandemics and enhance the overall performance of the U.S. health care system.

Introduction

In the waning days of 2019, global news outlets began reporting on a "mysterious viral pneumonia" infecting residents of Wuhan, China [2]. The first recorded death from what we now know as COVID-19, or the disease state resulting from infection with the SARS-CoV-2 virus, was a resident of Wuhan on January 11, 2020, and the first confirmed case of COVID-19 in the United States was on January 20, 2020 [3,4]. The World Health Organization declared COVID-19 a global pandemic on March 11, 2020, and since then, COVID-19 has claimed the lives of 828,000 Americans and 5.26 million individuals worldwide [103].

Although there were some examples of effective local, state, and national responses, there were critical issues and inconsistencies in the U.S. national pandemic response that resulted in delayed and insufficient availability of testing early in the pandemic, shortages of basic supplies including personal protective equipment (PPE), and strained health system capacity. Even with the advent of efficacious vaccines and therapeutics, COVID-19 and future novel viruses are expected to remain a significant global health threat. Both the direct and indirect effects of the pandemic have disproportionately affected communities of color in the U.S., as the virus has had a much higher mortality rate in Asian and Pacific Islander, Black, Latino, and Native American patients as compared to white patients [5,6,7]. Yet, even as the pandemic reveals or greatly exacerbates critical system fragilities, the conditions of the pandemic have also driven rapid progress in some areas, such as greater acceptance of telemedicine.

The Emerging Stronger After COVID-19 series of discussion papers, of which this paper is one, will examine nine sectors of the health care system, assessing both their existing vulnerabilities and their greatest opportunities for driving system-wide transformation toward effective, efficient, and equitable care for all Americans in the wake of COVID-19 [8].

Major Organizational Components and Interactions within the Health Product Manufacturers and Innovators Sector

HPMI research, develop, and produce a broad range of products and services that are critical to the health and well-being of people in the U.S. and around the globe. HPMI rely on a global supply network to provide components and ingredients to manufacture and operate these critical products and an extensive distribution system to ensure the delivery of these technologies across the U.S. and globally.

Despite the efforts of HPMI aimed at improving and extending lives, the COVID-19 pandemic has highlighted a range of vulnerabilities across the sector. This paper presents an individual assessment of the experiences and dynamics over the course of the COVID-19 pandemic through the lens of five specific sub-sectors — diagnostics, hospital supplies and personal protective equipment, Class III medical devices per the Food and Drug Administration's (FDA) classification system, therapeutics, and vaccines — to uncover the vulnerabilities and opportunities for sector-wide transformation (see *Figure 1*). Within each sub-sector's analysis of its experiences with COVID-19, the authors unravel the challenges each sector faced in continuing operations while responding to the domestic and global demands of the pandemic. Collectively, these vulnerabilities underscore the need for coordinated strategies to ensure the U.S. is well positioned to respond to the current and future public health crises and to enhance the sector's overall effectiveness, efficiency, and equity. As such, this paper concludes with a synthesized overview of priority actions that will aid in the navigation of future pandemics and other public health crises.

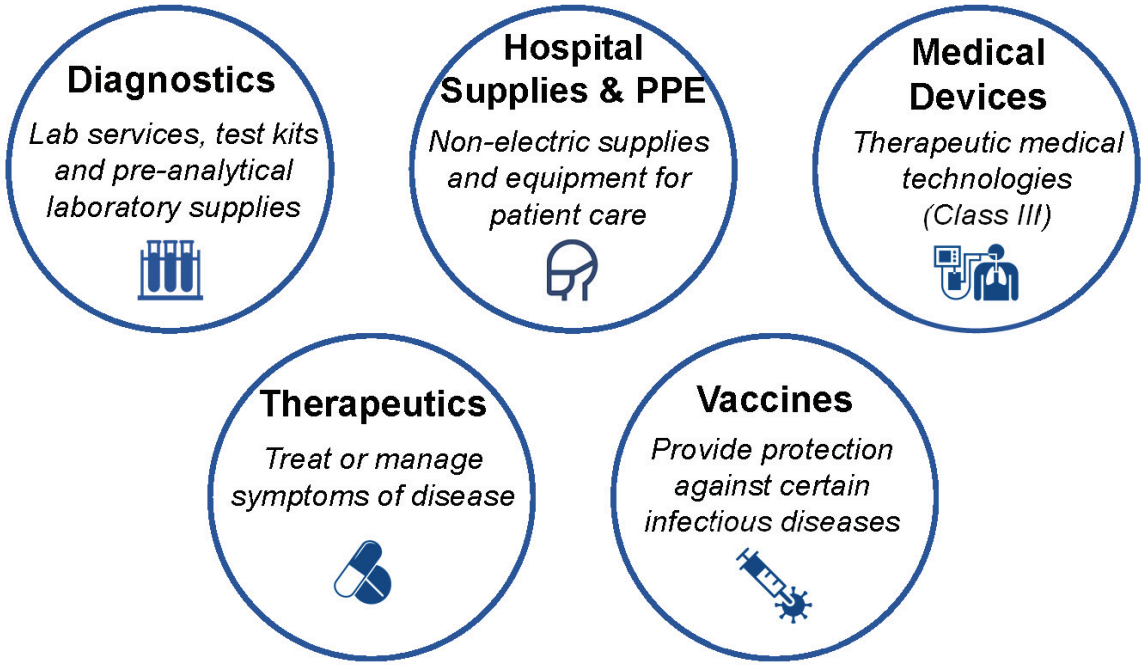


FIGURE 1 | Profile of the Health Products Sector

Individual Sub-Sector Analyses of COVID-19 Experiences, Dynamics Observed, and Vulnerabilities

Diagnostics

Overview and Response - Diagnostics

The diagnostics sub-sector offers a wide variety of products and services, including various diagnostics related to COVID-19. In this paper, the authors focus primarily on PCR molecular diagnostic testing, which is considered the gold standard in diagnosing whether a person is currently infected with the SARS-CoV-2 virus.

The diagnostics sub-sector includes manufacturers of test kits as well as pre-analytical supplies (such as swabs and tubes) and both public and private labs. Public health laboratories perform research, disease surveillance, emergency response support, and some diagnostic and reference testing for the public health agencies they serve, particularly for diseases with significant biosafety risks. Private labs include independent labs, hospital labs, and physician office labs. Some labs develop and validate their own tests that they perform as services (laboratory-developed tests, or LDTs), some labs run tests using manufactured test kits, and some do both. Private labs serve a broad array of customers, including physicians; patients; consumers; hospitals and health systems; employers; managed care organizations; biopharmaceutical, medical device and diagnostics companies; and governmental agencies.

At the start of the COVID-19 pandemic, a particularly prominent response shortfall was the failure to rapidly launch a comprehensive national strategy for the coordinated development and dissemination of tests for COVID-19. Then, in late January 2020, once the U.S. started to develop COVID-19 tests, national health leaders permitted only the use of government-created test kits, which were unable to be produced in numbers sufficient to match demand. Further constraining supply was the discovery of technical flaws in these test kits, which resulted in the decision to halt testing to rectify the issue [9,10,11].

As a result of these shortfalls, and the response to them, dynamics around diagnostics changed in at least two notable ways. The first was the somewhat sudden and widespread public awareness of the vital role diagnostics play in the nation's ability to understand and track the spread of COVID-19 — as well as to help treat and manage the disease.

Secondly, the U.S. saw a rapid expansion of COVID-19 testing capacity. Within days of the February 29, 2020 FDA guidance creating a pathway for private labs to develop and offer validated COVID-19 tests in addition to state and local public health labs, diagnostics companies responded by bringing tests to market and rapidly ramping up capacity ahead of determinations of payment or reimbursement [12]. Examples of ramping up capacity ahead of payment included purchasing equipment, complex machines, and testing and collection supplies; incurring costs for PPE; and investing

in additional site cleanings for protection against COVID-19. Companies that develop diagnostics expanded the accessibility of testing to reach as many people as possible, including health care workers, first responders, the hospital inpatient population, nursing homes, the elderly and the vulnerable, as well as those in underserved communities — through doctors, hospitals, other health care providers, retail pharmacy chains, drive-through testing sites and company websites.

Aside from COVID-19 testing, routine testing for non-acute conditions such as diabetes and cancer was paused during lockdown. Labs engaged with health care industry leaders and technology companies to raise awareness through national, large-scale campaigns such as Stop Medical Distancing [13], a program designed to explain the difference between social distancing and medical distancing to inform people about the importance of continuing to receive timely medical care.

Companies also offered employers and schools services for their return-to-work and return-to-school strategies. For example, certain labs offered return-to-work solutions, including some offerings using medical staff to administer health questionnaires when employees arrived, temperature screening, and specimen collection. One service offered employers access to testing solutions such as an at-home collection test kit, a finger stick antibody blood test, and flu vaccination services. The diagnostics sub-sector also developed novel laboratory-based tests, began offering at-home specimen collection and testing to expand access and reduce demand for PPE, and launched combination COVID-19 and flu tests.

Beyond greater testing capacity and access, new treatments and ultimately new vaccines, two of which have already received emergency use authorizations (EUA) and one FDA approval, are critical. To that end, many of the same laboratories and test kit manufacturers launched antibody tests, and some are providing testing to support COVID-19 therapeutic and vaccine research studies and clinical trials.

Vulnerabilities and Opportunities - Diagnostics

The increased attention prompted by the pandemic to the need for better testing capacity uncovered vulnerabilities affecting both public and private labs and in how public and private efforts are coordinated to create surge capacity.

As mentioned earlier, at the onset of the COVID-19 pandemic, demand outstripped supply, leading to longer times for people to receive the results of their tests. One of the reasons was due to a focus on government-created testing. There is acknowledgement that involving private-sector laboratories earlier would have allowed for a more rapid scale-up of testing capacity. If labs had begun receiving information earlier, when other countries were facing the crisis, they could have helped earlier [14]. Once private labs were allowed to provide testing under emergency-use conditions, the U.S.'s ability to test for the virus dramatically expanded. The authors of this manuscript believe that engaging both public and private labs early in the national response to COVID-19 would have helped scale up testing supplies and infrastructure more quickly.

The lack of excess capacity at labs, both public and private, was also evident during surges in COVID-19 outbreaks. Despite the sub-sector's significant efforts in the early days of the pandemic to increase the number of testing platforms available, the complexity of the machines, limited supply of machines and reagents, and staffing shortages made it difficult to scale quickly enough. Estimates of how many tests were needed varied widely [15]. Some experts predicted the need for millions of tests per day. However, some forecasts may have been referring to COVID-19 tests needed for diagnosis, screening and population-level surveillance, including both PCR as well as antigen tests, while others may have been referring to PCR tests, the gold standard for personal diagnosis. In any case, it was not until the Fall of 2020 that the U.S. may have begun to frequently hit 1 million or more diagnostic COVID-19 PCR tests performed per day, according to news reporting citing estimates from The COVID Tracking Project [16,105].

The response to the COVID-19 pandemic was also marked by fragmented and conflicting communication from various authorities and thought leaders. As the public searched for answers during the pandemic, they were confronted with no "single source of truth." This threatened to erode public confidence and likely resulted in people who did not need testing using up limited capacity [17]. In some cases, patients were unsure who should be tested, which test should be performed, and where a specimen could be collected. Further compounding the confusion was the fact that some doctors' offices were temporarily closed beginning in March 2020 [104]. As an attempt to mitigate some of these challenges, companies sought to help educate people about where and how to be tested, delivering important COVID-19 information to millions of people through social media, traditional media, and direct email channels, and sharing information with millions more via websites and through trade associations [18,19].

The single biggest vulnerability for the diagnostics sub-sector illuminated during the pandemic is the need for a fuller understanding of, and plan to address, the complexity and multifaceted nature of the global supply chain. While the diagnostics supply chain is often thought of as the test, the machine, and the result, in reality, it entails all the components necessary to collect the specimen, extract it, ship it, and test it — from nasal swabs to reagents, pipette tips, sterile tubes, dry ice, and complex machinery. Announcements of testing capacity based solely on machinal capabilities could be misleading without a reference to dependence upon the availability of necessary supplies. For example, while machines might be able to process a million tests per week, such a claim could be meaningless if there were only enough reagents to process a thousand tests. In addition to understanding that the supply chain is complex and contains many parts, it must be recognized that the supply chain is global. In the beginning of the pandemic, nasal pharyngeal swabs were being sourced primarily from Italy. When Italy was affected by the pandemic, obtaining swabs for U.S. use became a major challenge, not only affecting COVID-19 testing but also routine testing for conditions such as strep throat and sexually transmitted infections. Similarly, shutdowns in other countries such as China strained America's supply chain.

Finally, while speed is critical in a pandemic, so is continuing to monitor, maintain, and ensure the accuracy and reliability of tests. In the early days of the COVID-19 experience, a number of manufactured antibody test kits of poor quality were left unregulated and flooded the market, only to be withdrawn, further confusing the public and threatening to undermine confidence in tests and testing as a whole [20]. This included confidence in LDTs. Though, unlike test kits, LDTs continued to be regulated under the Clinical Laboratory Improvement Amendments (CLIA). This issue highlights the need for Congress to advance legislation to establish new, transparent validation pathways for all in vitro clinical tests to facilitate the prompt availability of accurate and reliable tests while preventing an influx of inferior products.

Hospital Supplies and Personal Protective Equipment

Overview and Response – Hospital Supplies and Personal Protective Equipment

The hospital supplies and personal protective equipment sub-sector develops products intended for use by physicians, nurses, hospital personnel, researchers, lab technicians, and others in health care. The sector serves a wide range of businesses including hospitals, clinics, and pharmaceutical companies. Products include a multitude of medical and surgical supplies, such as respirators, gowns, gloves, disinfectants, and sterilization products.

As soon as suppliers of health and safety products across the U.S. learned of the SARS-CoV-2 virus spreading in China in late 2019, they began putting measures in place to prepare. Manufacturers of hospital supplies and personal protective equipment began accelerating production and sourcing of PPE, notably respirators, in early 2020 [21,22]. A heavier than normal flu season was emerging in the Southern Hemisphere in the fall of 2019, portending a similar trend in the winter in the Northern Hemisphere. Signs of the novel and virulent coronavirus, in addition to unfolding natural disasters in Australia and the Philippines, triggered more steps for such manufacturers to prepare as requests for PPE started skyrocketing.

As the COVID-19 pandemic unfolded, manufacturers of hospital supplies and personal equipment were pressured to make appreciably more health and safety products. Global demand for N95 respirators and other respirators far exceeded the supply for the entire industry (rising as high as 20 to 40 times above normal levels). Some companies were prepared to handle normal fluctuations in supply and demand, having built and maintained excess surge capacity for worldwide disease outbreaks and natural disasters. Companies accelerated the process of adding new manufacturing equipment and production lines by diverting engineers, experts, and other resources from other departments to hospital supplies manufacturing efforts [23,24]. However, even with the addition of significant capacity, the unprecedented demand caused by the global pandemic outpaced production and supply.

By March 2020, production faced additional challenges as countries went into lockdown to help stop the spread of COVID-19 and companies halted nonessential operations. Manufacturers of health and safety products and suppliers of key raw materials assessed whether their operations fit government guidelines related to being critical to the pandemic response. Once that determination was made, they implemented safety measures such as those published by the U.S. Occupational Safety and Health Administration (OSHA) to reduce the risk of exposure for their essential employees and continued producing critical supplies such as PPE and hand sanitizer, among other products [25].

To further ramp up production of critical hospital supplies, the U.S. federal government began invoking the U.S. Defense Production Act (DPA) in spring of 2020, which gave the Executive Branch certain authorities to partner with and accelerate domestic industries during national emergencies. DPA authorities were used across several health care sectors including companies like 3M, Hill-Rom, Royal Phillips, and Vyaire Medical.

Health care providers also sought to extend the use of their PPE stocks by conserving respirators through clustering or isolation of patients with the same disease in order to support a crisis capacity strategy of not needing to change PPE after every patient contact. They also reused disposable respirators through decontamination procedures approved by the FDA via emergency use authorization (EUA).

Across suppliers of hospital supplies and personal protective equipment, collaborations played a critical role in the pandemic response. Many companies outside of health and medicine halted supply of their traditional products to supply PPE and other needed supplies for frontline health care workers and first responders. In addition, some initiated collaborations with companies to support the health care industry. A spirit of cooperation developed as hospital supply manufacturers connected with the automotive, industrial, or academic sectors to address various imminent health care needs. These collaborations with other companies to meet global challenges offer a model for potential future innovation.

Vulnerabilities and Opportunities – Hospital Supplies and Personal Protective Equipment

In the course of the sector's response to COVID-19, manufacturers of hospital supplies and personal protective equipment faced a number of trade challenges and export restrictions that impeded their ability to more quickly obtain critical raw materials and finished products such as PPE for health care workers and first responders. Access to raw materials was limited due to border closings and slowdowns in procurement, which highlighted the importance of supply chain diversity and resilience. These issues surface opportunities that include a more robust global supply chain, a comprehensive national response plan with visibility into stockpiles, and a framework to promote cooperation and incentivize information sharing sooner and faster during a public health crisis.

Trade challenges restricted the ability of hospital supply and equipment manufacturers to respond even faster during the pandemic. Some governments imposed restrictions on companies exporting the PPE made in one country to customers in other countries [26]. At one point during the pandemic, more than 40 countries imposed PPE export restrictions, and almost 165 countries imposed tariffs [27]. Trade barriers in some countries even extended to raw materials required to manufacture PPE. Occasionally, trading partners would retaliate by erecting reciprocal trade barriers for the same or other products or raw materials. Extensive, interconnected global supply chains in medicines and medical equipment makes this an issue faced by every nation around the world.

Limited supply chain diversity and redundancy among some producers also poses another sub-sector vulnerability. Certain companies experienced difficulty acquiring enough raw materials to consistently meet the needs for their factories. Many worked rapidly and concurrently to hire and qualify new vendors. Some manufacturers assumed additional costs for suppliers' expansion expenses or to expedite their new production equipment by air shipment. Moving forward, all manufacturers need to ensure that they have a broad supply chain of raw materials required for making health care consumables. Potential issues may emerge if manufacturers do not maintain a broad base of global suppliers, close to their factories, that can quickly increase production of raw materials when necessary. The global supply chain is only as strong as its weakest link, a reality experienced clearly early during the COVID-19 pandemic.

A granular view of what different states and localities needed at which time across the nation was lacking as manufacturers sought to optimize their production and distribution efforts. Some state health systems had adequate supplies and began preparing for future peaks of COVID-19, while others were working to obtain enough supplies for daily operations. Coordinated, national response plans with visibility to national, regional, and local stockpiles could enable a more effective and coordinated response to crises by shifting resources to outbreak hotspots.

Companies are subject to anti-trust laws that prevent them from sharing competitively sensitive information with competitors about their sales and distribution. One tool to help accelerate appropriate information sharing during a crisis is the use of a Voluntary Agreement overseen by the government under Section 708 of the Defense Production Act. This portion of the DPA gives the federal government the authority to work with the private sector to collect information and co-

ordinate the manufacturing and distribution of critical health care products and equipment during a crisis. This can be a particularly effective means to help efficiently distribute PPE across the sector. And the additional certainty, structure, and protections afforded by a Voluntary Agreement under Section 708 of the DPA may help encourage greater openness and provide an incentive for other manufacturers and distributors to participate.

Therapeutic Medical Devices

Overview and Response – Therapeutic Medical Devices

The medical device industry manufactures a wide variety of products. For the purpose of this paper, the authors focus on therapeutic medical technologies, generally falling into the FDA class III classification.

Therapeutic medical devices are typically devices that are introduced or implanted into the body percutaneously, through a body orifice or minimally invasive surgical incisions. As such, these devices are highly sophisticated and rely on intensive research and development phases, requiring significant time, resources, and financial investments. Having the potential of moderate to severe risk, therapeutic medical devices are subject to high regulatory requirements and require intensive pre-market prospective clinical studies and trials, as well as post-market clinical studies. Operations and clinical procedures involving medical devices may be categorized by a patient's medical condition and acuity: emergency operations and procedures for life-threatening conditions; necessary, but not urgent, procedures; and elective procedures. The application of these technologies often requires medical device industry representatives' assistance during procedures performed in hospitals and ambulatory surgical centers (ASCs).

Soon after the onset of the COVID-19 pandemic, medical technology industry representatives experienced a high variability of entry policies implemented by medical facilities to limit the potential of viral spread. These variable policies included SARS-CoV-2 polymerase chain reaction (PCR) or antigen testing requirements along with testing frequency and test sourcing, PPE sourcing (hospital versus medical technology company), representative physical positioning in procedures and operations, and inventory management. These policy variabilities and changing dynamics reduced the number of procedures at some health care systems and complicated the interactions of medical device representatives with clinical staff and patients. For example, some representatives had to source their own PPE due to unexpected changes in hospital inventory levels while also adhering to variable physical positioning mandates. These mandates, or rules regarding personnel access and distancing for representatives, not only varied significantly within hospital settings (e.g., operating rooms, catheterization labs), but between hospitals as well. Inventory management (sourcing, stocking, and maintenance of supply levels) was further complicated early on by changing medical device inventory management between medical technology representatives and hospital procurement and warehousing staff.

In response, many medical technology companies and an industry group (AdvaMed) created their own taskforces to work directly with hospital systems and organizations such as the American Hospital Association and Association of Perioperative Registered Nurses to standardize entry to health systems and procedure/operation participation while ensuring reduced COVID-19 exposure to patient, hospital personnel, and industry representatives.

Many of the hospitals affected by and, in many cases, overwhelmed by COVID-19 have also historically been involved in the execution of clinical studies and trials of medical devices. As early as April 2020, it was widely evident that initiation, execution, and continuation of new and ongoing non-COVID-19 clinical studies and trials were potentially distracting and interfering with the needed hospital human resources that were being repurposed from clinical research to COVID-19 patient management and care. Thus, medical device manufacturers and innovators worked with hospitals, research partners, regulatory bodies, and other relevant stakeholders to:

- assess the impact of COVID-19 on health care research partners and support them accordingly (e.g., reduction in non-COVID-19 clinical studies and in-kind representative support),
- temporarily pause clinical studies and trials where it was determined that local resources would be better allocated to COVID-19 activities,
- convert follow-up procedures (where possible) for those already enrolled in studies to remote methods to ensure participant, clinical site staff, and employee safety while maintaining proper sponsor oversite (via telephone or video conference whenever possible), and to widen the windows for follow-up from that designated in the protocol,

- document COVID-19-related impacts on clinical studies and trials, such as adverse events, COVID-19 diagnoses, and protocol deviations, and
- establish and engage ongoing communication with sites to ensure proper adjustment of activities as the pandemic situation continues to evolve.

To respond to the rapid increase in demand for intensive care unit (ICU) care beginning as early as February 2020, U.S. medical device manufacturers of ventilators and ICU monitoring equipment required over a five-fold increase in production to meet the U.S. and global demands [28,29]. This raised the need for business continuity planning as many of the products required components sourced from suppliers that were overwhelmed with demand. This rapid increase in demand resulted in a wide variety of integrated delivery networks (IDN) and manufacturer responses to deal with the pandemic. In terms of ventilators and ICU monitors, medical device competitors worked together to ramp up production, and non-medical device technology industries contributed by developing new manufacturing lines to provide the critical components needed for ventilator and monitoring equipment.

The COVID-19 pandemic thus produced unprecedented levels of collaboration across competitive manufacturers, where a common goal to fight the pandemic rose above the commercial concerns of collaboration. While engineers were making critical product decisions, the U.S. FDA was essential in streamlining the approval of needed technology to patients suffering from the pandemic by dedicating additional resources to the review process. Some examples included the approval of new non-traditional ventilator component suppliers, such as SpaceX, to provide against the growing unmet demand, and expedited approval of splitter ventilator systems that allowed more than one patient to be supported by a single ventilator [30].

After the initial shock of the COVID-19 pandemic and early adaptations implemented by the health care industry, medical device manufacturers worked with partners to evaluate how to resume elective procedures. To achieve this objective, three essential elements needed to be in place: material availability, people readiness, and hospital capacity.

Material Availability

Leveraging the supply chain momentum of the initial phase of the disease outbreak (between February and April 2020), manufacturers retooled supply chain processes by establishing cleaning and testing protocols so that medical testing sites were safe for employees, contractors, and logistics partners. Likewise, new collaborations were formed between various manufacturers and regulatory bodies to meet the rising demand for medical devices such as ventilators. This helped alleviate the fear of working among employees who could have been exposed to COVID-19 and successfully ramped up production in anticipation of demand. On the other hand, to deal with the non-uniform rescheduling and cancellation of surgical procedures in various states, manufacturers partnered with IDNs to determine the potential peak rates and dates of procedures by counties such that factory shutdowns and increases in production could be planned accordingly.

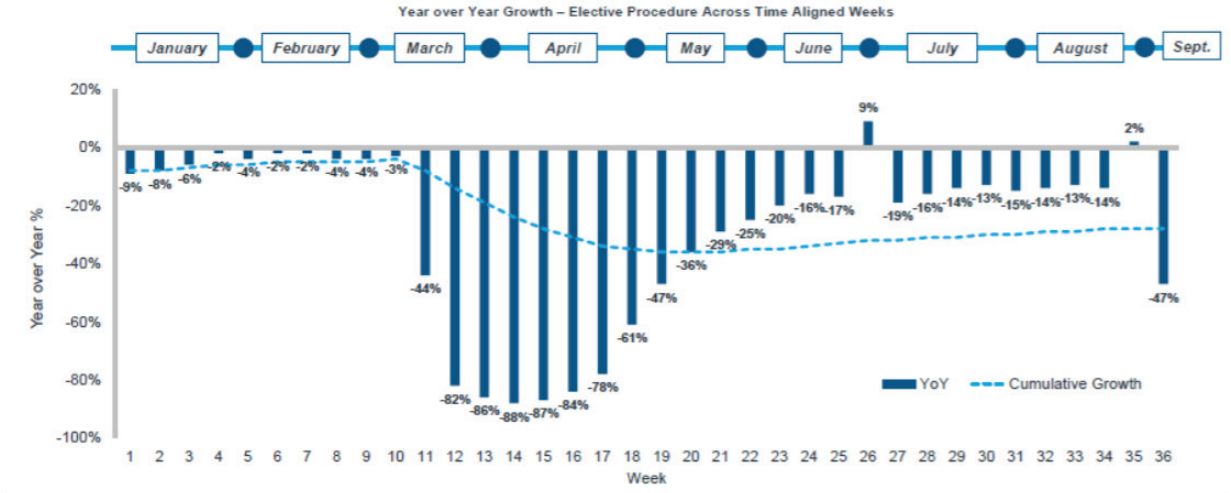
People Readiness

As noted in the diagnostics and therapeutics sections of this paper, patients' willingness to reengage with the health care ecosystem was a major challenge during the early to mid-stages of the COVID-19 pandemic (see *Figure 2*). More than two-thirds of Americans (68%) say they or someone in their household delayed or canceled health care services due to COVID-19 [31]. This was driven by multiple factors, including lack of medical knowledge about one's own existing health conditions, inconsistent and unclear messages from the government on the nature of the virus, and uncertainty in the economic climate and personal finances. Medical device manufacturers started campaigns such as "My Health Can't Wait," a public information effort and resource hub, designed to inform and raise awareness of patients to prioritize their health and reach out to their health care professionals about the risks of deferring care [31].

Hospital Capacity

A major milestone in the safe restart of health and medical procedures was realized when hospitals built up capacity and optimized resources to serve non-COVID-19 patients. This action paved the way for restarting medical device engagement with front-line procedures.

As the health care system began stabilizing in its response to COVID-19 by acclimation to new workflow adaptations and non-pharmaceutical interventions (NPIs), medical device manufacturers aimed to advance promising policies already in place, and recover clinical study enrollment where safety concerns for patients and staff were perceived to be reduced.



Source: IQVIA: Medical Claims Data Analysis, 2020; Week 1 2019 = W/E 1/11/2019; Week 1 2020 = W/E 1/10/2020, Week 36 2019 = W/E 9/13/2019; Week 36 2020 = W/E 9/11/2020

FIGURE 2 | Elective Procedure Volume Weekly Trends
SOURCE: IQVIA Institute Medical Claims Data Analysis 2020

Vulnerabilities and Opportunities – Therapeutic Medical Devices

As witnessed in other sectors of the health system, therapeutic medical device manufacturers experienced supply chain disruptions during COVID-19 due to shortages of materials, transportation limitations, and other factors. The lack of sufficient resilience and diversity in supply chains and distribution was, in large part, due to a focus on efficiency optimization and reducing redundancies that were prevalent prior to the COVID-19 pandemic. However, the rapid increase in the therapeutic medical technology demand overwhelmed suppliers and further highlighted the need for additional supply chain redundancy.

Information latency has been another major challenge aggravated by the pandemic. Given that medical device industry is highly fragmented with roughly 5,300-5,600 companies of various sizes, it can take months to develop an accurate industry-wide view on trends to evaluate the impact and recovery of COVID-19-related disruptions [32]. This is due to the lack of stable information sources, underinvestment in information technology systems by hospitals, and the over-reliance on human relationships such as those between surgeon and clinical representatives. Such factors resulted in information and decision decentralization. It is therefore challenging to make a data-driven decision on which devices to manufacture and where and how to distribute them during a health crisis. Due to the delegation of regulatory response to states, there were many different regulatory guidelines across the country, with varied reactions to the crisis overall. The absence of centralized structure left room for situations where states were bidding against each other to acquire limited medical devices and other materials. Greater communication and coordination are necessary to ensure the fair distribution of a limited set of materials during future public health crises.

More coordinated communication at the federal and state levels is also necessary as it related to continued operations of medical device trials and procedures during pandemic events. In the early stages of the COVID-19 pandemic, state and federal guidance differed in specificity. For example, the CDC focused on general guidance that could be applicable anywhere across the U.S., while some states initially ordered stronger mandates than federal guidance required. Some states mandated that if 25%+ of hospital beds were occupied by COVID-19 patients, then elective procedures would have to be put on hold, while others made it optional or subject to the discretion of the hospitals [33]. Furthermore, ASCs were not as impacted by the guidance and mandates issued (depending on the state) and hence continued business as usual. This variability required a nuanced approach in how both manufacturers and end consumers were able to engage with providers in each geography. Thus, there is a strong need for clear and fact-based guidelines from federal government and regulatory bodies during future pandemic events, allowing for clear action by all parties throughout health and medicine.

Therapeutics

Overview and Response – Therapeutics

Therapeutics refers to a class of pharmaceutical agents used for the treatment or management of disease symptoms. Manufacturers of therapeutics comprise a broad range of companies with differing therapeutic foci, operational capabilities, and global footprints. During the COVID-19 pandemic, therapeutics manufacturers worked to identify treatments for COVID-19 and associated secondary complications while continuing to deliver brand and generic medicines.

The development of therapeutics against COVID-19 initially focused, for the sake of speed and limited historic research in understanding coronaviruses, on repurposing existing medicines screened from within the industry's extensive treatment libraries. Early identified candidates included virus-directed small molecules such as direct acting antivirals (e.g., remdesivir), immunosuppressive and anti-parasitics (e.g., hydroxychloroquine), immune modulating monoclonal antibodies to target the cytokine response (e.g., Interleukin-6 monoclonal antibodies), and immune modulating small molecules (e.g., dexamethasone). These efforts were encouraged through accelerated regulatory pathways, as seen by FDA approval of remdesivir in October 2020 (only seven months after WHO declared COVID-19 a global pandemic, in contrast to an average approval time of 12 years in a non-pandemic context) [34]. In parallel to these efforts, preclinical research for novel therapeutics against COVID-19 rapidly expanded, with efforts in target definition, screening, and hit-to-lead optimization. These efforts include all modalities of biological therapeutics (e.g., small molecules, biologics, RNA-based therapies) of which there are over 300 candidates under consideration across various therapeutic approaches [35].

The COVID-19 pandemic provided an opportunity for institutions and organizations to work together in an effort to maximize biomedical research resources in testing preclinical compounds and prioritizing promising drug candidates. In April 2020, NIH launched the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership, which brought together government, industry, non-profit, philanthropic, and academic organizations [36]. Through ACTIV, NIH identified opportunities within COVID-19 therapeutics development in three areas: developing a streamlined manner to identify preclinical treatments, accelerating clinical testing of promising therapeutics, and improving clinical trial capacity and effectiveness.

Therapeutics manufacturers also invested in maintaining the flow of medicines and progressing treatments for COVID-19 by accelerating use of digital technologies. Machine learning techniques have been used to support faster and more precise drug discovery and development, including the identification of drug targets, responder groups, and new indications; qualification and quantification of surrogate endpoints; and acceleration of the time to drug formulation. Other tools have also critically afforded the opportunity to ensure patients still receive medical guidance and access to therapeutic treatments through opportunities to accelerate development via targeted patient recruitment and site optimization and faster clinical trials via remote monitoring.

Vulnerabilities and Opportunities – Therapeutics

Despite the efforts of many therapeutics manufacturers to address COVID-19, the sub-sector encountered challenges during the pandemic. Globally, there was a swift and extraordinary research response to address the unprecedented crisis. However, development of COVID-19 therapeutics was hampered by poor coordination, limited incentives for collaboration, and lack of prioritization of research questions and resources [37]. Within the U.S., the intent of the NIH ACTIV was to efficiently set priorities, design trials, and foster collaboration and coordination across clinical trial networks. Given that the U.S. clinical research enterprise does not function as a single national coordinated system, and since therapeutics innovators are often multinational corporations, many investigational programs to evaluate COVID-19 therapeutics were conducted external to ACTIV.

Without a system of national prioritization, inefficiencies in the research infrastructure essential to delivering therapeutics highlighted critical vulnerabilities that must be addressed in the coming years. The authors of this paper have chosen to focus on the vulnerabilities and opportunities that emerged during the early stages of the pandemic, namely in the areas of therapeutics development and clinical trial design. While there are additional vulnerabilities and lessons learned, they are not covered in depth in this paper.

These vulnerabilities included:

1. difficulty with providing patient care due to the significant decline in physical interactions between patients and their health care professionals, and
2. challenges to global operations and workforces due to factors such as the closure of national borders, export restrictions, disruptions

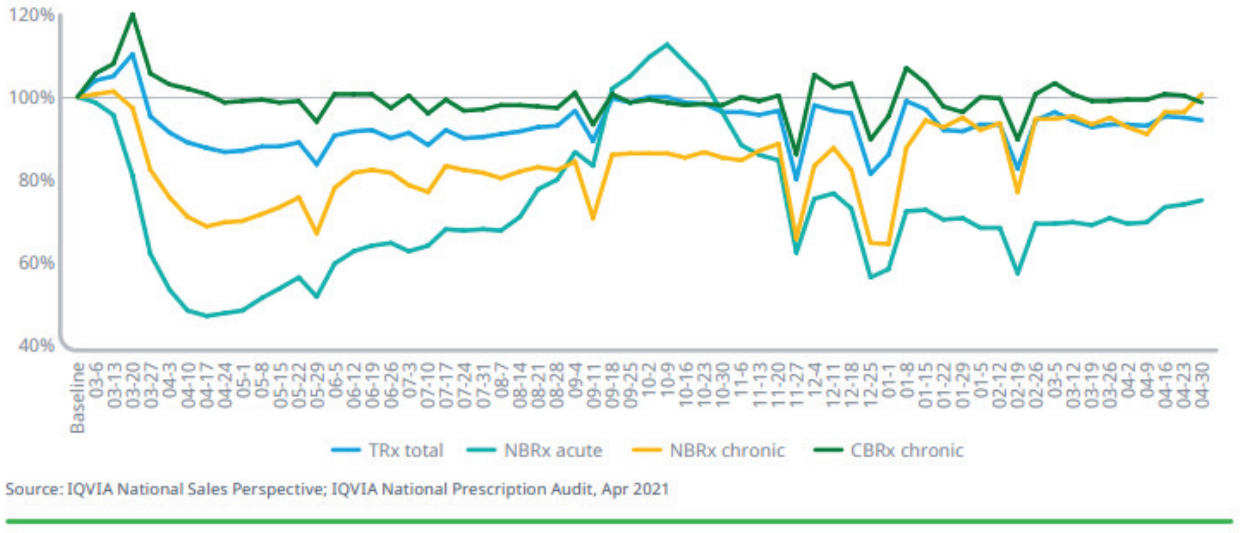


FIGURE 3 | Weekly Volumes of New Prescription (Rx) of Branded Therapeutics
SOURCE: IQVIA Institute National Sales Perspective and IQVIA Institute National Prescription Audit

to clinical trials and interactions with external innovation partners (especially small biotech enterprises and academia), and management of virtual global employee bases.

Relatedly, COVID-19 also highlighted the strains on the supply of equipment and therapeutics — including select critical generic drugs — particularly those used in the hospital setting.

In response to these vulnerabilities, the industry was able to utilize digital technologies to assist with the challenges of patient care. Similarly, the industry collaborated with regulatory bodies around the world to identify opportunities for flexibility within existing regulatory frameworks that allowed protocol modifications to ensure the continued development of therapeutics without undermining patient safety or clinical trial data integrity.

Difficulty with providing patient care

Physical distancing measures and the surge in COVID-19 cases across U.S. hospital systems impacted patient care and patterns of pharmaceutical usage in a number of ways. First, as initial concerns over pharmaceutical supply were raised early in the COVID-19 pandemic, many hospital systems and patients overstocked medicines for chronic diseases. In the course of the pandemic, there was also a significant difference in the number of new prescriptions for acute conditions versus new or existing prescriptions to treat chronic conditions, with demand for prescriptions to treat acute conditions far less than those used to treat chronic conditions. Prescriptions across all conditions by the end of March 2021 returned to 94 percent of the pre-pandemic baseline as per *Figure 3* [38].

Second, diagnosed and undiagnosed acute diseases and treatments requiring hospital visits (e.g., parenterally administered cancer treatments) saw a 33 percent reduction in prescriptions in April 2020 compared to April 2019 [39]. More than two-thirds of Americans (68%) say they or someone in their household delayed or canceled health care services due to COVID-19 [31]. This delay, caused by physical distancing protocols, patients' fears, and the health care system's focus on COVID-19, may lead to unintended health consequences in the future [40]. For example, during the pandemic, the weekly number of newly diagnosed cancers, spanning six types, fell 46.4 percent [41]. Additionally, parenterally administered non-oncology treatments saw even greater declines in volumes — 56 percent of the April 2019 rate in April 2020 [41].

Finally, therapeutics research relies on a seamless interface between investigators and clinical care providers. Local investigators enrolling potential subjects in a trial rely on clinical colleagues to refer patients for screening. At the height of the pandemic, hospitals, emergency rooms, and urgent care clinics were overwhelmed with managing acutely ill COVID-19 subjects, while many office-based general and specialty clinics were closed to reduce the risk of transmission of COVID-19. Similarly, researchers themselves were pulled away from working on clinical trials to provide clinical care where the pandemic threatened to overwhelm emergency medical systems. The health care workforce was stretched so thin that the American Medi-

cal Association even published resources dedicated to caring for caregivers on the front lines [42]. Given the logistical challenges associated with precise execution of investigational therapeutics trials, clinical colleagues may have viewed participation in a study as a distraction, while prioritizing clinical care for acutely ill subjects [37].

Challenges to global operations and workforce

Industry experts were concerned that drug production could be heavily impacted due to severity of the pandemic in Asia and Europe, two regions that manufacture significant quantities of ingredients and/or finished pharmaceuticals. Ultimately, therapeutics manufacturers were able to sustain the supply of needed drugs well through the pandemic as companies used dual-sourcing to lower the risk of local dependency and greater inventory strategies. However, the development of further redundancy in the system — including alternative shipping methods — is important for future pandemics.

Clinical operations were also heavily disrupted across the industry despite use of virtual platforms where possible. Estimates indicate as high as roughly 80 percent of non-COVID-19 clinical trials across the industry paused or stopped during the COVID-19 pandemic [43]. In light of this, the virtualization of clinical trials is a key opportunity area for further development and validation by agencies for the future. Finally, workforces were supported heavily to work remotely and the success of this unplanned pilot has accelerated a move toward distributed working across the industry.

Acceleration of digital technology use

Necessitated by physical distancing measures instituted to prevent the spread of COVID-19, the introduction of new or existing technologies to meet existing and emerging health needs have been integral to replacing previous physical interactions and enabling real-time clinical decision making, applying targeted treatments, and improving patient engagement. This uptake of digital tools includes rapid growth in telehealth utilization (43.5% of Medicare primary care visits were provided via telehealth in April 2020 versus less than 1% in February 2020), online pharmacy refills (total prescriptions filled online increased 25% year-to-year at start of pandemic), and virtual clinical trial monitoring. However, patients receiving a prescription for a new medicine for the first time (new to brand prescriptions) via telehealth services were down from between 18 percent to 44 percent relative to pre-pandemic rates depending on the specialty [38,44,45]. These figures demonstrate the significant decline in number of patients being both diagnosed by a health care provider and subsequently receiving a prescribed medicine where appropriate.

Regulatory and reimbursement frameworks that required physical visits to health care professionals led to the underutilization of digital solutions that already exist and potentially disincentivized further expansion of these technologies. Whether this level of digital interaction can be maintained after the pandemic subsides and whether the initial positive effects are sustainable in a post-pandemic setting will in part depend on clarity of reimbursement for provider networks and the acceptance of these research modalities within clinical trials regulations. Early indications for telemedicine indicate a reduction in use from the peak of the pandemic but a new base level of 1 percent of all health care engagements done via telemedicine before the emergence of COVID-19 versus 9 percent as of April 2021 (see *Figure 4*). The broad implementation of telehealth during the COVID-19 pandemic is more thoroughly discussed in this paper's companion pieces focusing on care delivery [46] and digital health (forthcoming).

Changes to FDA guidance and protocols

The FDA demonstrated a willingness to listen to challenges faced by the health care system and acted rapidly to provide guidance on emerging needs by introducing adaptability in addressing COVID-19-mediated clinical trial impacts. This included patients directly receiving investigational medicinal product (IMP) at their home as opposed to the IMPs being provided at the research site by the trial staff, virtual clinical trial monitoring, local bioassay assessments (as opposed to the standard centralizing assessments), tele-visits, home nursing, and remote electronic access for data source verification. These nimble flexibilities were applicable both for COVID-19 and non-COVID-19 therapeutics and vaccines.

Prior to the COVID-19 pandemic, the FDA had encouraged use of novel clinical trial methodologies to mitigate the effect of missing data (e.g., due to patient withdrawal from trial participation) on trial integrity and endpoint assessment. These same methodologies can also be used to analyze datasets of on-going clinical trials disrupted by the pandemic. In June 2020, FDA released a guidance document to provide recommendations to sponsors on methods to consider for minimizing the impact of COVID-19 disruptions on trial integrity [47]. Some of these disruptions have led to "unforeseen intercurrent events; that is, they affect either the interpretation or the existence of the mea-

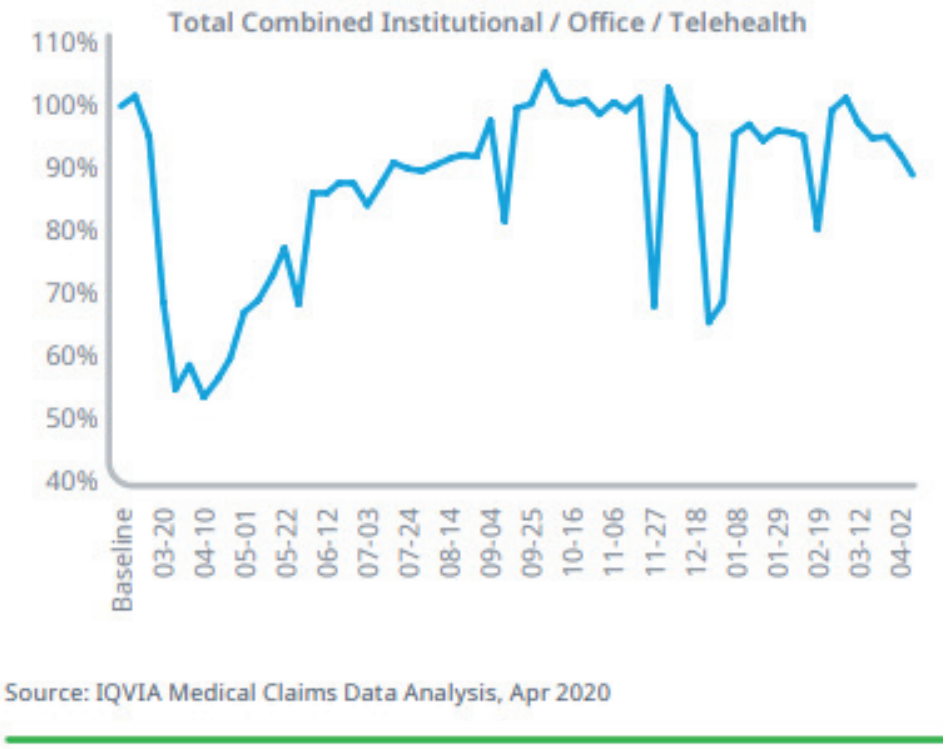


FIGURE 4 | Telemedicine Use Among Healthcare Provider Organizations
SOURCE: IQVIA Institute Medical Claims Data Analysis, April 2020

surements associated with the clinical question of interest while others prevent relevant data from being collected and result in a missing data problem." [48] The estimand framework developed by the International Council on Harmonization provides strategies to assess and mitigate the risk of seriously compromising the integrity and interpretability of clinical trials, as also acknowledged by the FDA and the European Medicines Agency [49,50,51]. These considerations provide guidance on the handling of missing data due to, "for example, the inability to perform important procedures like biopsies during the pandemic or government restrictions," which prevented subjects from attending scheduled visits [48,52].

Furthermore, suitable adaptive design methodology is available to, for example, implement unplanned interim analyses of an ongoing trial with the aim to better assess the impact of the disruptions due to the pandemic or help resizing the trial in terms of its duration or sample size [52]. Finally, supportive approaches could aim to integrate data from external sources, supplement the control arm, or merge trial data with results from previous or concurrent trials [53]. Regulatory authorities will need to consider approvals based on a higher-than-normal level of uncertainty and use relevant post-approval data to complement the pre-registration study(s), where feasible.

Vaccines

Overview and Response - Vaccines

The field of vaccine development includes manufacturers and innovators involved in the research and development, manufacturing, sales, and distribution of vaccines.

Vaccine discovery and development is a failure-prone, lengthy, and expensive process, frequently costing over $1 billion from start to finish, and manufacturing is technically challenging and expensive. A large portion of vaccine development projects never make it to regulatory approval. Despite substantial industry and government efforts, only about two dozen vaccines have been successfully developed and deployed in the last 100 years [54]. In spite of these challenges, vaccines have made significant contributions to global health, including the eradication of smallpox and near eradication of polio [55]. Additionally, they have been credited by the CDC for saving nearly $406 billion in po-

tential health care expenses associated with prevented disease and $1.66 trillion in total societal costs, like loss of productivity, since 1994 [56].

When SARS-CoV-2 emerged, the field had no off-the-shelf vaccines available for this entirely new virus. However, the U.S. government, U.S. regulators, and numerous global biopharmaceutical companies acted quickly and collaboratively to accelerate the vaccine development process, which traditionally takes a decade or more, to yield over 200+ distinct vaccine candidates, 11 candidates in Phase 3 trials, and two approved for distribution with Emergency Use Authorization (EUA) and one fully approved as of October 1, 2021 [57,58,59]. Developing, manufacturing, and distributing a vaccine in a year is a landmark achievement in health care. The high efficacy against serious disease of the first three candidates (over 90% effectiveness) places the COVID-19 vaccines on par with other highly effective vaccines in use today (e.g., measles) [60,61].

While vaccine developers are solving many challenges in the development process, it is also essential to anticipate potential supply chain and distribution issues. A recent report by the U.S. Government Accountability Office highlighted the challenges of scaling up mass production of the vaccines, which would interfere with the effective rollout [62]. Given the need for hundreds of millions of vaccine doses in the U.S. and billions globally, there is a dire need for manufacturing capacity, achievable through new capacity or by shifting capacity from other products. Furthermore, there is a limited supply of products such as glass vials, stoppers, needles, and syringes that are typically not rate-limiting but proved at various times in the last year to be unexpected bottlenecks for the immensity of scale required [63]. Beyond goods and materials, pandemic-related disruptions such as changes in worker availability and export restrictions could severely impact the supply chain's ability to meet the demand. Lastly, in terms of distribution, it is important to recognize that there are different requirements for storage and transportation depending on the vaccine. For example, the vaccines from Pfizer/BioNTech and Moderna preferably require freezing at - 94 degrees Fahrenheit and -4 degrees Fahrenheit respectively for safe storage, which pose meaningful challenges when trying to inoculate the global population. Both vaccines can be stored at higher freezer temperatures, but for a limited duration [64,65]. The vaccines from Johnson & Johnson and AstraZeneca, on the other hand, can be stored at refrigerated temperatures [66]. As the industry moves into the critical phase of delivery, supply resilience will need to be front-of-mind for every link in the value chain.

While upholding the highest safety and regulatory standards, several factors facilitated the delivery of multiple vaccine candidates to the public in 18 months. One factor was the use of new biologic platforms that had been developed by investments made in past years, supported by reliable intellectual property systems (e.g., mRNA and adenovirus platforms). Additional factors included:

- earlier and frequent engagement with regulators,
- expedited regulatory reviews,
- vast investments in private and public resources for vaccine development and delivery,
- enhanced collaboration within and between public and private sectors (see *Table 1*),
- at-risk manufacturing at commercial scale well ahead of entering the vaccine candidate into human trials, and
- compression of Phase 1/2a dose ranging studies and manufacturing timelines.

Beginning in May 2020, coordinated government support for promising vaccine candidates was provided through Operation Warp Speed (OWS), a partnership among the Department of Health and Human Services, the Department of Defense, and private-sector companies. The aim of the partnership was to "accelerate the development, manufacturing, and distribution of vaccines, therapeutics, and diagnostics for COVID-19" without compromising on safety, quality, or efficacy [67]. OWS has impacted vaccine development through over $10 billion dollars of support for vaccine development efforts, manufacturing capacity scale-up, and at-risk manufacturing, and through coordination with FDA on technical matters and with Department of Defense on vaccine distribution channels. As of February 2021, the White House COVID-19 Response Team assumed the responsibilities of OWS. Government support also continues to be available through the participation of NIH Vaccine and Treatment Evaluation Unit trial sites in Phase 3 clinical trials for preventive vaccines, such as the Moderna mRNA vaccine and the Johnson & Johnson vaccine [68,69].

Vulnerabilities and Opportunities – Vaccines

In responding to COVID-19, the field of vaccine development contended with several vulnerabilities brought to the fore by the pandemic. The authors of this paper have chosen to focus on the vulnerabilities and opportunities that emerged during the early stages of vaccine manufacturing and innovation, namely in the areas of discovery, development, and clinical trial design.

Company	Collaboration	Vaccine type	Description
Johnson & Johnson	Beth Israel Deaconess Medical Center; BARDA	Non-replicating viral vector	DNA sequence for coronavirus **spike protein** delivered via adenovirus type 26 vector
Pfizer	BioNTech	mRNA	Genetic instructions for the coronavirus **spike protein** are encoded in mRNA, delivered via lipid nanoparticle
Moderna	NIAID; Lonza	mRNA	Genetic instructions for the coronavirus **spike protein** are encoded in mRNA, delivered via lipid nanoparticle
AstraZeneca PLC	Oxford University	Non-replicating viral vector	DNA sequence for coronavirus **spike protein** delivered via chimpanzee viral vector
GlaxoSmith-Kline	Sanofi	Protein-based	Coronavirus-derived protein produced in insect cell lines, extracted and delivered alongside an adjuvant to target **spike protein**
CanSino Biologics	Precision NanoSystems	Non-replicating viral vector	DNA sequence for coronavirus **spike protein** delivered via adenovirus type 5 vector
Sinovac	Dynavax	Inactivated virus	Combination of chemically inactivated SARS-CoV-2 and immunological agent to target **spike protein**
Novavax	Takeda, Emergent BioSolutions, Serum Institute of India	Protein-based	Coronavirus-derived protein produced in insect cell lines, extracted and delivered alongside an adjuvant to target **spike protein**

TABLE 1 | Examples of collaborations which emerged during COVID-19
SOURCE: Department of Health and Human Services. 2020. COVID-19 Vaccines. Available at: https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html (accessed December 19, 2020).

While there are additional vulnerabilities and lessons learned in areas like distribution and supply chain capacity, they are not covered in depth in this paper.

One potential risk in the traditional approach that has been adopted for vaccine development for COVID-19 is the limited diversity of candidate vaccine designs as a result of the limited variety in their antigen targets. Specifically, all the vaccines are monovalent, relying on one antigen protein, which is SARS-CoV-2 spike protein [70]. If the protein target had yielded safety or efficacy issues in humans, all candidate vaccines would be at risk of being unstable and unsafe. Though Phase 3 testing has proven that this is not the case, industry-wide vaccine development effort might have faced an overall lower degree of risk if incentives were in place to drive increased target diversification. The parallel pursuit of alternative protein antigens, multivalent vaccines, and T-cell vaccines would have mitigated the risk and increased the overall likelihood of success. A related vulnerability that may yet play out is the possibility of mutations occurring to the spike protein, this would impact the entire collection of vaccines. Several variants of the virus have now emerged, including variants with one or more mutations to the spike protein. New vaccines or boosters accounting for these variants will need to be brought forward quickly if needed.

The limited diversity of approaches in vaccines R&D also reflects the limited diversity of biopharmaceutical R&D overall. This limited diversity is understandable in the context of market dynamics, where the industry disproportionately invests in diseases for which reimbursement and pricing is well-established such as cancer, autoimmune diseases, and rare diseases. However, the lack of investment into understanding virus strains impedes the industry's understanding of future pandemics, making vaccine development challenging, and reflects a more general lack of investment in basic and translational science and technology. Areas in need of substantially increased government investment include (Note: Examples provided refer specifically to pandemic preparedness and are not encompassing of all research needs):

- **Fundamental human biology** – e.g., in the case of pandemic preparedness, better understanding of the innate immune response to infections and how it differentiates "friend vs. foe"
- **Therapeutic modality research** – e.g., the use of RNA therapeutics for rapid response to pandemic threats either as antiviral or as vaccine
- **Human toxicology science**
- **Manufacturing science** – especially of new therapeutic modalities
- **Clinical trial design** – e.g., modifications to design that allow for non-placebo-controlled trials in conjunction with the use of data science to generate better controls and identify other ways to assess comparator arms

While the areas listed above are critical, it is equally important that investments encourage diversity with regards to the entire clinical trial ecosystem, from enhanced, culturally appropriate recruitment of trial participants to recruitment and training of diverse investigators and site coordination staff. It is important to incentivize research in primary care and, further, ensure that trials address a diverse and representative population. Achieving this requires a commitment to identifying new investigators, trial sites, and more sustained commitment in underrepresented communities to establish trust and confidence in the clinical trial process.

A second vulnerability illuminated by COVID-19 involved data sharing and application across governments, global health bodies, and industry parties. Historically, the stakeholders involved in vaccine development, manufacturing, and distribution were siloed, preventing data from being shared across organizations to maintain a competitive advantage. Furthermore, the available data on prevalence and impact of diseases were inconsistent and of low quality. This led to the creation of the COVID-19 R&D Alliance, which was organically established by heads of pharmaceutical R&D companies to improve information sharing, helping vaccine developers move quickly and with confidence without jeopardizing competitiveness or intellectual property rights [71]. While this proved effective as a short-term solution to data sharing during the pandemic, a longer-term arrangement is not assured. Therefore, it is important that the lessons learned from the Alliance be codified to inform the response to future infectious disease outbreaks.

In standard vaccines development, Phase 1 studies test for safety and tolerability of the candidate vaccine and yield data on immune measurements of antibodies and T-cells that are induced by the vaccine. In subsequent, lengthier Phase 2 and 3 studies, vaccine efficacy, or protection from the disease is measured.

At the end of a Phase 3 study, it is possible to quantitatively relate the magnitude of immune measurements to the magnitude of efficacy, thereby providing a roadmap to other vaccine developers and an ability to move subsequent vaccines forward more quickly than would otherwise be possible. Consideration should be given to how best to rapidly construct immune-efficacy correlates (i.e., the nature and magnitude of the various forms of immune induction by the vaccine, and how they predict its efficacy), and how best to incentivize early vaccine developers to share these roadmaps to accelerate solutions across the full industry ecosystem. In the case of the present pandemic, such roadmaps have not happened. Additionally, there is an opportunity to apply advanced analytics to real-world data to accelerate clinical trials and deliver vaccines faster.

The COVID-19 pandemic also highlighted the opportunity to incorporate alternative clinical trial designs to randomized control field trials to deliver a vaccine more quickly. Once randomized clinical vaccine trials are underway, time to completion is inversely proportional to the incidence rate of infection. For example, when there is less freely circulating virus, the clinical trial takes longer to complete, and the inverse is also true. An alternative form of trial, the human challenge trial, has been used for some viruses, including influenza and respiratory syncytial virus. These human challenge trials involve exposing consenting subjects to a weakened strain of the virus in controlled and safe environments. While the data generated has limitations (given the use of weakened strains) and there are ethical considerations (given that subjects are intentionally infected), challenge trials are substantially smaller and faster than randomized control trials since they are uncoupled from disease incidence and many believe that careful adoption of them would benefit society. The UK government has been an early adopter of human challenge trials, investing £33 million to carry out the first human challenge trials to accelerate a COVID-19 vaccine [72]. While well worth exploring, it remains unknown as to whether these types of trials could fully replace more traditional Phase 3 studies.

Today's vaccine clinical trial protocols enroll subjects to be randomized equally between an arm that receives a vaccine and an arm that receives a placebo. Recruiting large numbers of placebo patients takes time, is expensive, and raises ethical questions about giving individuals a placebo in regions of high disease burden. Using real-world data (structured and unstructured electronic health records, claims data, imaging, genetics, and laboratory data) in a circumstance-matched (propensity-matched) set of subjects to construct an "external control arm" (sometimes called "synthetic control arm") would reduce the need for as many placebo-dosed subjects. The net effect would be to reduce the time to recruit and conduct the trial and reduce the number of subjects that are intentionally left unvaccinated. Additionally, with EUAs issued to the Moderna and Johnson & Johnson vaccines and full authorization to the Pfizer/BioNTech, there is an ethical dilemma in keeping individuals in a placebo arm for other randomized clinical trials, especially considering that companies are intentionally enrolling vulnerable populations that are especially in need of protection by a vaccine. Several alternatives to placebo controls exist, such as head-to-head randomized trials that compare a novel candidate vaccine with a previously authorized vaccine, or multigroup platform trials [73]. Synthetic control arms are another alternative; however, the technical and regulatory hurdles of a synthetic control arm are significant and would need to be addressed to gain broader adoption.

Inequities Observed During COVID-19 by Health Product Manufacturers and Innovators

The COVID-19 pandemic has highlighted the acute and chronic nature of disparities in the U.S. health care system. Most well-known are racial disparities in rates of COVID-19 infection, hospitalizations, and mortality. As shown by several recent studies, Black, Latino and Indigenous peoples have been disproportionately impacted by COVID-19, and factors such as age, gender, economic, and environmental factors further exacerbate these effects [74]. For example, in a recent study involving 2,595 patients tested at a Milwaukee hospital for COVID-19 from March 12 through March 31, 2020, Black patients were 5.4 times more likely to test positive than other races. Males had increased risk of testing positive (1.5 times more likely than women) as did people of increased age (twice as likely if over 60 years old) [77]. Strikingly, ZIP code explained 79 percent of the overall variance in positive test results. Economic variance across ZIP codes further delineated outcomes. "After adjusting for ZIP code, Black patients were 1.9 times more likely to require hospitalization, while those living in poverty were 3.8 times more likely." [75]

Certain comorbidities such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, heart

disease, obesity, sickle cell disease, and type 2 diabetes, which disproportionately affect some minority communities, have been identified as factors contributing to poorer outcomes for patients with COVID-19. Some additional diseases have limited reported data but might contribute to an increased risk for severe illness from COVID-19, including asthma, cerebrovascular disease, hypertension, immunocompromised states, and liver disease. Minority communities are particularly susceptible to these diseases due to the interplay of structural inequities across the social determinants of health (SDoH) including housing conditions, economic stressors, and limited access to nutritious food.

As major drivers of health inequities, SDoH have been the topic of much discussion. Yet, they are seldom addressed in the design or implementation of systems of health care. For example, despite efforts described earlier in the diagnostics section of this paper to expand the accessibility of testing through site identification on the internet, drive-through testing and at-home kits, certain underserved communities experienced disparities in access to COVID-19 testing. Part of the reason is that these solutions do not solve the issue of patients without access to a car, or of those without a home address where a specimen collection kit could be mailed. Lack of access to the internet was also a barrier for some patients. Similarly, the lack of predictability of reimbursement and the variety of cost and out-of-pocket burdens on patients likewise has a direct bearing on these health inequities. These examples suggest the need for careful analysis of the entire range of factors impacting health status, along with acknowledgement of and strategies to address implicit bias in health care, and health access as health solutions are designed and rolled out.

Another set of critical issues that have been given considerable attention is the inclusion of communities at greater risk of infection, hospitalization, and death from COVID-19 in clinical trials of diagnostics, therapeutics, and vaccines. COVID-19 vaccine sponsors have faced difficulties in recruiting diverse populations for Phase 1 and 2 trials (despite a desire to do so), resulting in approximately 90 percent of volunteers being white [76]. This illuminates the overall lack of diversity in the clinical trial process, especially of Black, Latino, and Indigenous populations. Without representative patient populations enrolled in clinical trials, results may not fully reflect the clinical response (efficacy, side effect profile, etc.) that will be seen in the real world.

Attempting to increase inclusion in clinical trials during the pandemic has had its own unique set of challenges. However, some of the strategies developed prior to and during the pandemic in addition to innovations in design and execution of clinical trials serve as a solid foundation. These modifications include the use of virtual visits and monitoring, ensuring inclusion and exclusion criteria do not inadvertently exclude diverse patients, and increasing capacity of minority investigators and centers serving minority communities. Fundamental changes are necessary to make representative inclusion sustainable.

Trust and Communication Across All Sub-Sectors of Health Product Manufacturers and Innovators

Trust and communication were vulnerabilities that appeared across all five sub-sectors discussed in this paper during the COVID-19 pandemic. Inequities across HPMI point to a larger problem of lack of trust in health care, national preparedness, and public health countermeasures. The biopharmaceutical industry and health care overall are amongst the lowest-rated industries in the U.S. for overall public sentiment (along with oil and gas and the government), though polls indicate that there has been an improvement in the public perception of the biopharmaceutical industry during COVID-19, due largely to the role the industry has played in responding to the pandemic [77,78].

As HPMI mobilized to address challenges across supply chain networks, the politicization and associated spread of misinformation related to repurposed or new therapeutics and critical supply availability negatively impacted efforts to slow or halt the spread of COVID-19. The touting from some quarters as to the health benefits of newly developed and existing therapeutics (e.g., azithromycin, hydroxychloroquine, chloroquine, REGN-COV2) to treat symptoms associated with COVID-19 reflected inconsistencies in communication of efficacy from clinical trial data and, in some instances, were bolstered by issuance of EUAs. However, the FDA revoked some EUAs after certain drugs were proven to provide no clinical benefit and were shown to increase risk [79]. Although industry responses strived to maintain public confidence in private-sector COVID-19 countermeasures, various communication obstacles remained. During the pandemic, primary modes of industry engagement and communication with the public were limited. Consumers received downstream updates from the federal government on COVID-19 safety and containment measures and guidance on the purchase of PPE [80,81]. However, these communication streams, among others (e.g., so-

cial and mass media platforms and health department COVID-19 sites), contended with misinformation about vaccine development procedures, COVID-19 test quality and availability, and PPE distribution.

A considerable increase in counterfeit masks and respirators posed an additional obstacle to maintaining and fostering public security and trust. Shortages in these critical supplies led to increases in the marketing of unsafe and substandard masks and respirators to hospitals, clinics, and the public at large [82]. With counterfeit supplies posing a threat to industry standards and the health and safety of those who wore these substandard masks and respirators, companies and federal agencies took quick action to alert health care workers, first responders, consumers, and the general public [83,84]. In addition, companies and federal agencies moved quickly with warnings about false rapid COVID-19 tests and unverified vaccine research and development protocols to protect consumers and to combat what was being deemed as "an erosion of public trust in science." [85,86]

A lack of trust in biomedical science is especially acute in subsets of minority communities due to a history of discrimination in science, misguided R&D practices by various stakeholders, and a lack of access to accurate information. This problem exacerbates the fact that these populations are at the highest risk of infection and death from COVID-19 [87]. Many sources point to scarce representation of and discrimination against minority populations across the STEM workforce as sources of mistrust [88]. Despite the nation's STEM workforce having grown more diverse over time, numbers in these fields are still far below the level of diversity represented in the general population [89]. These concerns have also extended to the low levels of diversity relative to the general population in clinical trial enrollment for therapeutic procedures and drug development — an issue the FDA continues to address in its most recent guidance on enhancing the diversity of clinical trial populations [90,91]. Finally, memories of medical injustice, as was present in cases such as the Tuskegee syphilis study, still raise suspicion among minority communities most affected by health disparities [92]. Acknowledgement of and action to address key structural inequities that have perpetuated mistrust of biomedical science in minority communities should remain a sector priority as it considers ways to enhance effectiveness of future pandemic responses.

Information and activities that address building trust in biomedical science need to be more diligently studied. Diversification in clinical trial enrollment and disaggregation of clinical trial data signal efforts to better represent the general population in the design, implementation, and efficacy of solutions for pandemic preparedness. Additional considerations for indemnification coverage frameworks, along with viable mechanisms to compensate individuals in the event of unintended harm from emergency use of rapidly developed products could promote wider public confidence in industry efforts and sustained sector action to ensure equitable distribution of pandemic resources as a priority. Sub-sectors across HPMI — whether or not they have been primarily or peripherally cited for practices that have contributed to public mistrust — have a responsibility to assess and reform their practices if necessary to become more trustworthy among those (especially minorities) who would use their products and services. The need for consistent and coordinated communication and proactive, innovative actions to combat mistrust and misinformation is clear. Policy makers, the HPMI sector, and the health care industry need to work together to solve these problems that have been present all along but were exacerbated and made more evident by the COVID-19 pandemic.

Consolidation of Priority Actions Needed Across the Field of Health Product Manufacturing and Innovation

Across all sub-sectors of HPMI, several vulnerabilities exposed by COVID-19 have been described above. These vulnerabilities suggest a clear set of critical areas of opportunities, seen in *Figure 5*.

1. **Support for Science:** Encouraging the diversity of basic scientific approaches toward research, development, and implementation to support the development and implementation of diagnostics, vaccines, medical equipment, and treatments for coronavirus infections, influenza, infectious diseases, and other global health threats.
2. **Data Sharing:** Setting standards and processes for data collection, sharing, and application across governments, global health bodies, and industry parties in ways that are mutually beneficial but that also maintain competitive dynamics.
3. **Supply Chain Resiliency, Stockpiling, and Surge Capacity:** Establishing supply chain and infrastructure redundancy, including the availability of "ever warm" manufacturing capacity and stockpiling.

FIGURE 5 | Opportunities for Sector-Wide Transformation

4. **Regulation and Reimbursement Clarity and Flexibility:** Enhancing efficiency and effectiveness through modernizing regulatory processes and providing clarity on coverage and reimbursement to support and incentivize innovation.
5. **Coordination and Communication:** Driving improved domestic and international (private sector and government) stakeholder coordination to enable consistent and transparent communication.
6. **Minimizing Substandard Offerings:** Addressing and mitigating the emergence of substandard, falsified, and counterfeit PPE, treatments, and diagnostics during a public health crisis.

The authors of this paper have proposed a set of discrete federal policy actions to address these vulnerabilities and improve efficiency, efficacy, and equity across the U.S. health care system. Supporting detail pertinent to each HPMI sub-sector is below each overarching policy area.

Identified Policy Opportunities for Health Product Manufacturers and Innovators

Support for Science

Proposed policy: The budget proposed by the President of the United States to Congress should contain unified policy across agencies such as NIH, BARDA, FDA, Centers for Medicare and Medicaid Services, CDC, National Institute for Occupational Safety & Health, OSHA, NSF, VA, DOD, and DARPA, with guidance for allocation across areas of greatest need, including basic science, applied technology, advanced development of diverse scientific approaches, and training of medical technologists and academic labs to improve response time and probability of technical success in future pandemics. Every year the budget should contain a section that lists projects and initiatives that would encompass a domestic, unified preparedness agenda across federal agencies. It would provide guidance to Congress across appropriations committees and serve as both a strategy document and a clear de-

scription of what is required to ensure preparedness for ongoing and future pandemics.

In the U.S., the NIH funds most medical research dedicated to uncovering the root causes of disease through research grants to more than 2,500 institutions across the country. The research undertaken by NIH-funded investigators is a critical foundation for scientific discovery, enabling health care companies to build on this research and develop new health care products. Furthermore, NIH-funded research often allows otherwise risky and massive investments of money, time, and manpower to be focused on shepherding medical treatments through regulatory approvals.

Investment in fundamental research and new technologies to address potential future pandemic viruses would substantially improve America's public health preparedness. For example, such investment could include sequencing strains of coronavirus that are incubating in zoonotic species such as bats to better understand potentially emerging diseases. The availability of protein sequence data for dozens of strains could yield a dataset that allows vaccine innovators to act well in advance of a pandemic.

Within the therapeutics and vaccines sub-sector, government funding should focus on a few select programs per biological target for a given indication. Sustained investments in both early-stage research at NIH and advanced development activities at the Biomedical Advanced Research and Development Authority (BARDA) are needed. This approach would encourage pursuit of a more diverse set of vaccine and therapeutics candidates, leading to a higher probability of successful approvals. The new science entity proposed by President Joseph Biden in Spring 2021, known as the Advanced Research Projects Agency for Health (ARPA-H), is currently under design and may also provide funding channels appropriate for investment into innovative, breakthrough medical treatments [93,94].

There are also challenges to large-scale manufacturing for each vaccine platform. The government should invest in fundamental research in manufacturing at scale on new platforms of interest (e.g., viral vectors, mRNA, novel adjuvants) with the capability of responding to multiple pandemic threats. It is critical that these investments target improved yield, speed, and purity of these scale-ups by also focusing on the accompanying technologies that support the production of vaccines at scale, such as the purification and bioprocessing machinery used in the engineering of vaccine modules.

Federal investment should extend beyond biological and biomedical science disciplines. For the hospital supplies and personal protective equipment sub-sector, sustained funding in materials science can bolster innovation of new formulations of materials that strengthen the integrity and effectiveness of vital supplies such as PPE and test swabs. By inventing alternative materials with similar or improved chemical and physical properties as their predecessors, these materials can be readily manufactured "on shore" and the sector can avoid global supply disruptions.

For the diagnostics sub-sector, support for science must involve funding for more training programs to address shortages of medical technologists and to train academic lab staff to assist in pandemics in compliance with CLIA.

Proposed policy: Address the lack of diversity in the clinical trial system by reducing barriers to enrollment of representative minority populations, those from low socio-economic backgrounds, and children in clinical trial recruitment, and increasing the numbers of diverse clinical investigators, coordinators, and site staff.

COVID-19's disproportionately devastating impact on minority communities in the U.S. has focused attention on the underrepresentation of communities of color in clinical trials. This underrepresentation is due to systemic obstacles as discussed in the Trust and Communication section of this paper, from lack of diversity in clinical trial investigators, historical events leading to distrust of the medical establishment, and socioeconomic factors such as inadequate access to affordable transportation to clinical trial sites and childcare. As there are a variety of causes of this problem, it will take a variety of policy solutions, including investment in and greater partnership with diverse communities, to achieve meaningful change.

While the FDA has developed guidance documents focusing on enrollment practices and Health and Human Services (HHS) has developed an action plan on inclusion of demographic subgroups in clinical trials, a broad range of stakeholders, including trial sponsors, need to take additional efforts to expand clinical trial diversity. The health care industry needs to create dialogue and relationships with a more diverse array of stakeholders to advance initiatives aimed at successfully recruiting underserved and underrepresented patients and apply new tools to increase enrollment of diverse populations in clinical trials. Clinical trial practices can mitigate barriers by leveraging lessons from

successful recruitment efforts and educating communities about the importance of clinical trials and the importance of diverse participation. Targeted outreach efforts can be employed to increase the diversity of investigators and site staff. Additional efforts to broaden trial participation could include conducting decentralized clinical trials that ease burdens on participants, ensuring that materials are translated and culturally appropriate, and making necessary investments to conduct trials with community health centers and physically locate sites where communities of color reside. Foundationally, HPMI can remedy diversity blind spots by recruiting talent that represent a variety of perspectives and cultivating the early entry of people from diverse backgrounds into STEM fields through science apprenticeships and scholarship programs.

Data Sharing

Proposed policy: The Federal Trade Commission, Department of Justice (DOJ), FDA, CDC, the Office of the National Coordinator for Health Information Technology (ONC), and the Office of Inspector General (OIG) should develop a framework for industry stakeholders to enter data-sharing agreements during national emergencies for pre-clinical and clinical development results in a way that is mutually beneficial while also maintaining competitive dynamics and addressing privacy concerns.

Impediments to sharing of patient data among hospitals and health care systems is not a new challenge related to the pandemic. However, the pandemic has highlighted the imperative to address the barriers to the flow of these data, not just for future pandemics, but throughout health care.

In collaboration with HPMI, regulators such as the Federal Trade Commission, DOJ, and relevant HHS agencies such as the FDA, ONC, CDC, and OIG should create a legal and regulatory structure that incentivizes data sharing and ensures trust and competition by maintaining traditional protection of intellectual property and trade secrets, but allows HPMI to share other manufacturing, safety, and early efficacy and validity data amongst themselves and with the federal government. This type of agreement may require review of antitrust guidelines and applicable privacy laws, and the timing of data sharing should be done in consideration of competitive dynamics. Where there are international interfaces for data sharing, there should be clear protocols established and alignment of the governance and requirements to enable relevant data to be shared in a protected and secure manner between different territories. Data sharing at the international level must take into account that several countries have data localization and privacy laws that would restrict the export and sharing of personal data.

For the medical devices sub-sector, there is an opportunity to enable and encourage information sharing via consortia and government guidance to improve data completeness, accuracy, and latency. Affordable Care Act initiatives today mandate this type of sharing in primary care and eye care — which could be expanded to hospital products for the betterment of all parties. Unfortunately, the health care industry is currently moving in the opposite direction. Many states have begun to discuss restricting the sharing of data, and California has passed a Consumer Privacy Act which allows consumers to opt out of the sharing of their information [95]. It is critical that these types of regulations do not extend to health data that is used for research and clinical purposes (in a HIPAA-compliant manner). During times of crisis, this type of data sharing will also help to identify safe opportunities for localized therapy for medical devices.

For the hospital equipment sub-sector, as companies worked with government agencies like the Federal Emergency Management Agency (FEMA) and others to distribute products, agencies needed to ensure that companies' competitive information remains proprietary and is not being shared with other companies. Stronger protection of sales, supply chain, and distribution information in emergency scenarios may encourage greater openness and an incentive for other manufacturers to participate.

In addition, more clarity to manufacturers and distribution networks about supply levels at health care systems and other essential sub-sectors from federal, state, and local governments would help appropriately targeted and coordinated PPE distribution during an emergency. During the pandemic, many networks could have benefited from needs-based assessments across various levels to inform distribution plans. A federal dashboard or control tower structure would provide more visibility to companies regarding where the distribution of their product is needed most.

Lastly, many of the drivers of inequities in health outcomes are poorly understood. The potential exists to strengthen data collection, sharing, analysis, and application, specifically regarding demographic data needed for public health analyses. Platforms and repositories such as the National Interoperability Collaborative, which accelerated understanding in other

areas of study such as rare diseases, may be applicable in informing a response to future public health emergencies. Strengthening demographic data collection and diversity of participants could inform a more equitable approach to distribution of supplies as companies work to support communities most in need.

Proposed policy: In cooperation with FDA, CDC, and ONC, develop guidelines and data standards for health authorities and appropriate industry stakeholders to report and accept pre-defined data during national health emergencies to allow for more rapid and effective responses.

Within the therapeutics, vaccines, and medical device sub-sectors, data standards should be adopted to enhance analytics of baseline epidemiologic trends and to improve the interpretability of therapeutics developed to treat COVID-19. Furthermore, within the therapeutics sub-sector, mechanisms should be in place to facilitate sharing compound libraries that enable rapid screening.

For the vaccines sub-sector, it is essential to establish a platform with a standardized format for vaccine innovators to share safety and efficacy data following early trials to increase the overall availability of data and to improve the statistical accuracy and efficiency of vaccine creation, with appropriate limitations for patient data protection and protection of proprietary information. Further, with the availability of vaccines, real-time data capture should be facilitated, which can be vital in vaccine surveillance and monitoring post-market safety.

Although the diagnostics sub-sector reports public health data about infectious diseases to local health departments and federal entities on a regular basis, the COVID-19 pandemic highlighted the opportunity for data-reporting systems and procedures that are faster, more complete, and more transparent — and not duplicative or demanded in non-standard formats. To that end, demographic data needed for public health analyses, but not necessary for performance of laboratory testing, should be collected and reported directly to public health authorities by health care providers who have direct contact with patients, not by laboratories that typically have no such direct contact with patients and to whom such data is typically not reported by ordering health care providers. Laboratories should report test result data in a standard format to public health authorities to help with contact tracing without duplication of reporting to multiple entities for the same jurisdiction. Public health authorities should be adequately resourced and have the technical capabilities to receive required data in standard electronic formats and should not demand reporting of data that they are not capable of receiving in such formats.

Supply Chain Resiliency, Stockpiling, and Surge Capacity

Proposed policy: Ensure federal policies encourage manufacturers and laboratories to invest in and maintain sufficient redundancy at all levels of the supply chain across geographies and distribution channels.

Federal policies, particularly relating to trade, customs, and manufacturing, should encourage manufacturers to maintain sufficient redundancy at all levels of the supply chain, including ensuring the reciprocity of the free flow of medical goods across borders. Within the diagnostics, medical devices, and hospital supplies and personal protective equipment sub-sectors of HPMI, a resilient supply chain requires a holistic view of all components needed from start to finish. For example, having an abundance of testing machines will have minimal positive effect on a public health crisis without supplies to collect specimens or reagents to run the tests. There must be coordination between every link in the supply chain. To accomplish such coordination, mechanisms and infrastructure should be established for standardized communication of supply needs and supply availability among and between manufacturers, their customers, and government, where appropriate. Congress and the current Presidential administration should invest in an IT system that has pre-identified supplies and suppliers that can be called upon in real time to assess the supply chains and surge capacity of suppliers.

To avoid shortages, products must be continually shipped and received. In the early stages of the COVID-19 pandemic, global air cargo throughput decreased ~20 percent year-to-year, primarily due to a sharp decline in passenger demand and the grounding of commercial air traffic, creating logistical challenges never seen before [96].

In addition, contingency supply chains and dual mechanisms play critical roles in ensuring redundancy. Policies should incentivize manufacturers to build and maintain robust supply networks to mitigate the risk of delayed shipment or other breakdowns along the supply chain (including local supply chains to avoid geographic bottlenecks during future crises). Border closures or delays due to changes in customs procedures

or decline in the number of personnel to conduct inspections can impact essential supplies from reaching their destination in a timely manner. Correspondingly, all stakeholders should consider which critical components should be stockpiled and/or manufactured in the U.S. and at what volumes to ensure patient access, if global logistics are interrupted. Consideration should be given to whether a North American "compact" might expand manufacturing and strengthen supply chains across the U.S., Canada, and Mexico.

Particularly for medical supplies and equipment relied upon by health care providers, policy makers should evaluate the public health implications of trade restrictions for flow of goods through their borders. Countries that erect export restrictions may score a short-term win, but supply chains inevitably adjust and flow around them, leaving "islands" with less access to supplies. Additionally, public-private partnerships should be developed to ensure mobility through prioritized and effective distribution of limited resources. Government planners that work with manufacturers with the capacity to manufacture at scale, with access to needed raw materials at scale, and with access to existing and robust distribution channels are able to get product quickly to those who need it the most. Centralized government direction during a crisis and public-private partnerships can help ensure that supply chain systems and distribution networks focus on public health priorities. Governments should facilitate the appropriate collection and analysis of distribution and use data to help ensure resources are properly distributed to those who need it the most.

For the therapeutics and vaccines sub-sectors, policies should protect and preserve industry's ability to procure active pharmaceutical ingredients and medical components from multiple, diverse sources, which are essential to ensuring patient access to life-saving and preventative medicines, medical technologies, and treatments.

Proposed policy: As has been suggested in previous reports, Congress should appropriate robust, sustainable funding to incentivize the building and maintenance of continuous "ever-warm" manufacturing capacity and stockpiles [97]. The HHS Assistant Secretary of Preparedness and Response should lead a process to describe what supplies, medicines, and devices should have an "ever-warm" manufacturing capacity able to respond to immediate spikes in demand. This process should work in coordination with updates to the Strategic National Stockpile strategy, which focuses on which products should be maintained by the government and which should be maintained in vendor-managed inventories that are funded by the government.

The U.S. Strategic National Stockpile and state stockpiles, which are designed to provide supplies, medicines, and devices during public health emergencies, should be viewed as an insurance investment ready in the event that a catastrophic disaster strikes. If not used in the short term, it is not a wasted investment, just as buying home insurance is not viewed as a wasted expenditure.

Particularly for responding to pandemics, epidemics, and natural disasters, excess surge capacity is critical to meeting the rapid and enormous spike in demand for all manner of health care products and services. For example, a way to be prepared for the next inevitable health crisis is to invest in a national "stockpile" of diagnostic machines and platforms at key public and private labs that are up to date, running, and calibrated, with spare capacity supported by the supply chain architecture [98]. This includes investing in both private and state-run health labs for seasonal and pandemic event operations. Equally, policymakers should provide clear guidelines on required stockpiles of emergency use equipment to be maintained at provider sites, manufacturers, and elsewhere. Additionally, a consistent and coordinated approach, based on public-private collaboration, should be taken to allocate hospital capacity (e.g., beds) for emergencies and non-crisis-related ongoing procedures in a standardized fashion to reduce morbidity and mortality in future crises.

Relatedly, within the therapeutics and vaccines sub-sectors, multi-stakeholder efforts should focus on increasing capacity for biologics and vaccines manufacturing to shorten the period between product development and its broad availability to the public. Emergency global procedures for rapid repurposing of existing facilities, as facilitated by virtual inspections and concurrent reviews by national health authorities using previously agreed upon criteria, would support such efforts. The government should expand use of "warm base" facilities that provide a minimum level of funding and task orders each year to ensure availability of priority facilities during a pandemic.

For hospital supplies and medical devices stockpiles, procedures should be developed to ensure replenishment of expired products. National stockpile programs need a robust and transparent distribution framework,

accurate data, and tactical plans to ensure supplies reach those in need. Policymaking efforts at both federal and state levels should be oriented toward ensuring the availability, integrity and funding of stockpiles for future health emergencies.

The federal government could encourage these capacity-building efforts by incentivizing the industry to invest in new capacity-increasing technologies. Modular manufacturing, robotics, and digitalization of supply chains will be critically important for future pandemics. Investments in digitalization would enable supply chains to improve end-to-end visibility, which will help in making better and faster trade-off decisions. For instance, while 3D printing is currently expensive, it can quickly change production capacity. It would also help in vaccine and therapeutic research by speeding up processes and producing the necessary tissues for testing. 3-D printing of biopharmaceuticals could likewise be introduced to help with shortages during disruptions.

Regulation and Reimbursement Clarity and Flexibility

Proposed policy: Provide clarity on indemnification coverage for rapidly developed products in cases of emergency use to boost the public's confidence in being vaccinated and in their government.

HPMI and various others in the policy arena have long held that a comprehensive indemnification coverage framework is critical across the vaccines, therapeutics, medical devices, and hospital supplies sub-sectors — especially in emergency use pandemic situations. For instance, COVID-19 vaccines are critical to control the pandemic. This is a major undertaking requiring a significant portion of the world population to be vaccinated [99]. Achieving this objective requires a high and sustained level of public confidence in these vaccines. Key tools in supporting this confidence are no-fault vaccine injury compensation programs [100]. These are not intended to provide a "free pass" for willful misconduct, criminal activities, or violations of regulatory requirements. While pharmaceutical companies developing COVID-19 vaccines are working to follow all applicable laws, regulations, safety protocols, and principles of good manufacturing practices designed to ensure the safety of vaccines, liability protections ensure that there is an appropriate framework in place to address the unique risks posed by a pandemic.

Governments must assure availability of public health EUA regulatory powers as part of their public health laws to enable rapid access to substantially equivalent supplies, such as PPE, without regulatory delays.

Proposed policy: Provide regulatory and reimbursement flexibility in defined circumstances to encourage greater use of innovative approaches, such as emerging technologies, aimed at increasing health care system effectiveness and efficiency. Regulation should be transparent and provide clear guidelines on when flexibility is permitted, such as during national health emergencies.

Within the therapeutics sub-sector, there is a need to improve clinical trial data acquisition and enhance clinical trial participant recruitment and retention with the incorporation of some of the flexible trial modalities introduced during the early stages of the COVID-19 pandemic, when physical distancing protocols were at their most strict. Methods such as home nursing study visits for drug administration or endpoint evaluation, direct to patient shipment of investigational medicinal product, remote electronic medical record access, remote monitoring, greater acceptance of real-world evidence, electronic informed consent, and methods for imputation of missing data should be assessed for their potential as tools to improve trial operations outside of a pandemic situation.

For the vaccines sub-sector, it is important to adapt regulatory policies to support innovative trial design. Specific proposals include:

- convening of an ethics committee to evaluate the use of human challenge trials to significantly accelerate vaccine creation timelines,
- adoption of synthetic control arms that draw on real-world data to simulate comparator sets of patients such that control arms are smaller, and
- leveraging of advanced analytics to accelerate standard randomized controlled studies through predictive modeling of incidence rates.

It is imperative to modernize reimbursement in the U.S. to offer the opportunity to increase patient access and reduce costs across the health care system. One way to support this reimbursement modernization is to make permanent the reimbursement flexibility instituted during the COVID-19 public health emergency. Changes should be implemented as appropriate across the entire health care spectrum, not just for prescription drugs, so that the significant savings from appropriate

medication usage can be deployed in other payment systems.

To encourage the use of value-based pricing models, it is important to incorporate analyses that use real-world evidence for outcomes-based reimbursement processes and for decisions regarding labelling and standard of care. For the vaccines sub-sector, achieving this objective would require incentives and regulatory guidelines in support of the development of validated, real-world endpoints for registrational studies and real-world evidence generation for reimbursement. Use of this data is highly dependent on their validity, traceability, and ability to meet clinical endpoints agreed on with regulators.

In addition, traditional government contracting mechanisms are not suited for rapid development and manufacturing activities needed during a pandemic. Echoing previous recommendations [97], Congress should consider providing additional authorities to relevant agencies (e.g., BARDA, DOD) that would allow for flexible "plug-and-play" contracts to support the development of multiple vaccine and therapeutic candidates.

Lastly, for the diagnostics sub-sector, there should be a quick path to reimbursement at levels appropriate for what a pandemic requires. In addition, diagnostics should be covered by public and private health plans without patient cost sharing, medical management, or utilization limitations, and they should be available at a reasonable price that enables sustainable access and continued growth of capacity. Since COVID-19 and other pathogens may be transmitted by asymptomatic individuals, coverage exclusions for asymptomatic individuals — or for purposes such as enabling return to work or school or for surveillance — are counterproductive and should be avoided. Since delays in result delivery times during pandemics are typically caused by spikes in demand and supply shortages, varying test reimbursement based on result delivery time will not decrease result delivery time. Punishing labs by cutting reimbursement during demand spikes will exacerbate result delays due to reduced resource availability. In addition, such policies could have unintended consequences, such as a disparate adverse impact on certain patient populations, for example, patients in rural areas who are geographically more distant from labs. Therefore, such variable reimbursement proposals should be avoided.

Coordination and Communication

Proposed policy: Develop a robust national strategic plan for pandemic preparedness and response. The plan should highlight key elements of comprehensive supply strategy, coordinated communication to the public, regulatory laws to align industry responses, and mechanisms to pressure test pandemic response structures.

A clearly defined public health defense strategy would help address the dynamically changing demands and needs at different stages of a crisis, and suggest how to balance the tradeoffs between quality, speed, and cost at key junctures. Components of this plan should articulate a strategy for how to use various tests and how to effectively distribute stockpiled hospital products in times of public health emergency. Establishing early, continuous, and action-oriented dialogue between industry and the various HHS departments during public health crises is critical to making quick decisions, especially to ensure timely and equitable access to testing, vaccines, therapeutics, and medical devices.

For the diagnostics sub-sector, the focus at the start of the pandemic response was on PCR molecular diagnostic testing, which was and continues to be important as the gold standard for use in diagnosing COVID-19. However, other forms of testing also became available that can play important roles in certain scenarios, including point of care, antigen, and antibody tests. Outlining a clear role for each test at each juncture of a public health crisis — and engaging both public and private labs from the outset — furthers public understanding and efficient resource deployment. In addition, it took too long to scale up low-cost, widely available testing for surveillance. The focus on quality was and is important, but there also needed to be a focus on quantity for lower-cost alternatives and point-of-care testing. While these tests may have lower reliability, they still serve a significant purpose for screening and surveillance.

Testing is also used in vaccine development. As noted in an October 2021 white paper from the American Clinical Laboratory Association (ACLA): "Assessing the effectiveness of a vaccine is directly related to its ability to induce immunological response. Tests measuring anti-SARS-CoV-2 IgG concentrations and neutralizing antibody titers to the SARS-CoV-2 virus targeted to spike protein and receptor binding domains have been used in the phase 2 and phase 3 clinical trials to correlate with the efficacy of vaccines under development." Therefore, as the science evolves, as the ACLA puts it,

"There may or may not be a role for similar SARS-CoV-2 serological assays to determine the efficacy, durability, and the need for a booster dose." [102]

Finally, allocation of tests and supplies should be accomplished through coordination and communication of capacity and need rather than through mandates. It is important to recognize and accommodate different suppliers' and service providers' operational models — specifically, national labs that work across the country versus in a state or region.

For the hospital supplies and medical devices subsectors, there is an opportunity in the U.S. for this plan to assess which items and quantities of supplies are set aside for emergencies and to call for the development of systems for assuring stockpiles are at adequate levels to assure minimum response expectations required for various disaster scenarios, including pandemics (see the section of this paper titled Supply Chain Resiliency, Stockpiling, and Surge Capacity). Globally, what most plans are lacking is a metaphorical appendix within each plan of the needed goods and services for frontline workers to conduct their daily duties. Adopting a methodology that helps ensure a continuous supply that is able to be used prior to its expiration date, perhaps with incentives to encourage manufacturers to participate, is an important option for public-private partnership.

Laws like the DPA are important tools in the U.S. government's response to a public health emergency. However, when invoking the DPA, the playing field among competitors is not always even. The federal government might consider calling on all manufacturers in a sector to participate in accelerating manufacturing so that a few companies are not disproportionately burdened. Involving all entities within the health product manufacturers and innovators sector might indeed help accelerate increased access to additional levels of much-needed supplies.

It is critical that a national preparedness plan be developed in coordination with an international joint task force that would explore opportunities for global regulatory cooperation ("pandemic proofing") and for coordinating global scientific messaging. For development of the national preparedness plan as well as for development of proposals for sector-specific responses, an advisory panel composed of qualified and representative government and private-sector subject matter experts might offer a formal mechanism to present a consistent, evidence-based set of recommendations for the pandemic's response.

In addition, efforts to increase medical awareness should be implemented in a clear, consistent, and localized manner to avoid confusion, uncertainty, and misinformation while boosting public confidence in seeking care. This is relevant for all health care sub-sectors that depend on a citizenry remaining actively engaged in behaviors that stem the spread of disease, especially during a pandemic. For the diagnostics sub-sector, in particular, it is important that providers, test kit manufacturers, laboratories, and the public have clear, timely, and actionable guidance and recommendations from government authorities and thought leaders regarding prioritization of testing and how to access it.

Proposed policy: Encourage greater collaboration through partnerships between governments and the private sector.

In early April 2020, the NIH, FDA, BARDA, FEMA, academia, and pharma R&D leaders met to identify how to rapidly accelerate the response to COVID-19. A key outcome was the formation of the ACTIV public-private partnership. In this partnership, all industry partners agreed to contribute their clinical trial capacities toward the shared goal of bringing forward therapeutic and vaccine candidates. This partnership was different from others in the past in that regulators were involved from the very beginning, enabling a speedier formation [36]. Another example of fruitful public-private partnerships during the pandemic is the Gates Foundation/Wellcome Trust/MasterCard COVID-19 Therapeutics Accelerator [101], where up to $125 million in seed funding helped to identify, assess, develop, and scale up new treatments for COVID-19. The partners are committed to equitable access, including making products available and affordable in low-resource settings. However, ongoing and enhanced government engagement across public and private partners should be encouraged. This translates to federal agencies taking a holistic approach to connecting with hospital supply manufacturers, raw material developers, and trade associations such as the ACLA and the Association of Clinical Research Organizations at the start of a public health crisis. Such partnerships should be encouraged as they have the potential to accelerate the development of new vaccines, therapeutics, diagnostics, and hospital supplies, and broaden their reach.

Minimizing Substandard Offerings

Proposed policy: Establish a procedure to update, communicate, and monitor standards for diagnostics, hospital supplies and equipment, and medical devices over the course of a pandemic to ensure product integrity and reduce circulation of substandard and/or counterfeit products.

There should be government- and industry-wide efforts to monitor, mitigate, and prevent sub-standard, falsified, and counterfeit medicines, health care products, and health care services during public health emergencies.

For the diagnostics sub-sector, public confidence in testing is in part dependent upon the awareness of the manner in which tests have been validated for their intended use and public education regarding different regulatory pathways that can be taken for validation. While there should be a mechanism for tracking the status and quality of both manufactured test kits and LDTs that have been submitted to the FDA for EUA, there should also be a mechanism for tracking LDTs that have been validated by laboratories under CLIA. Congress should advance legislation to establish new, transparent validation pathways for all in vitro clinical tests to facilitate the prompt availability of accurate and reliable tests while preventing an influx of inferior products, which we saw during this pandemic's early stages.

Finally, for the hospital supplies and personal protective equipment sub-sector, export restrictions and global supply shortages led to a significant increase in fraud, counterfeiting, and price gouging of certain products as health care customers and governments sought to procure the supplies and equipment they needed. Governments should coordinate with law enforcement, customs authorities, and the private sector to set science-based performance standards that prevent fraudulent and counterfeit products from appearing in global and domestic markets. The effect can be dramatically improved when stakeholders in this arena also employ advanced barcoding and authentication systems to address counterfeit issues.

Conclusion and Vision for the Future

The global COVID-19 pandemic has tested the HPMI sector and led it to respond and adapt to crisis in a multitude of ways. While the pandemic has revealed significant vulnerabilities, it has also demonstrated important resiliency, adaptability, and contributions of the sector.

The COVID-19 pandemic also has highlighted several opportunities for needed change. By leveraging the collective learnings and experiences gathered from across the sector, reforms and actions can be developed to ensure strengthened post-pandemic health care. With careful reflection, the COVID-19 pandemic can act as a much-needed catalyst for actions to correct long-present issues in the American health care system.

As health product manufacturers and innovators, the authors of this paper propose greater investments in areas of unmet need, updated guidelines that incentivize innovation, processes to improve cooperation and coordination, and reward structures that incentivize desired behaviors among stakeholders. Such priority actions will fundamentally change the context in which manufacturers and innovators operate, resulting in improved effectiveness, efficiency, and equity overall. For example, incentives for HPMI to invest in areas of high unmet need that may have otherwise been financially unsupportable are crucial. Additionally, sustained funding and relevant trade policies will enable those manufacturers and innovators to add much-needed redundancies to their supply chains without negatively affecting operational efficiency.

The authors of this paper recognize that putting these action priorities into practice will be challenging. However, with the right operations, resources (e.g., funding, personnel, material, technology) and prioritization mechanisms, they will result in a more efficient, efficacious, and equitable health care ecosystem. As health product manufacturers and innovators, we are committed to doing our part in achieving these priority actions with a spirit of service, deeply vested in assuring that our nation's patients, frontline health care workers, and society more broadly have access to the diagnostics, hospital supplies and personal protective equipment, devices, therapeutics, and vaccines they need.

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DOI

https://doi.org/10.31478/202201b

Suggested Citation

Mammen, M., V. Narasimhan, R. Kuntz, F. Lewis-Hall, M. Poul, and A. Schechter. 2022. Health Product Manufacturers and Innovators COVID-19 Impact Assessment: Lessons Learned and Compelling Needs. *NAM Perspectives.* Discussion Paper, National Academy of Medicine, Washington, DC. https://doi.org/10.31478/202201b.

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Acknowledgments

The authors would like to thank **Mahnoor Ahmed,** National Academy of Medicine; **Christopher Allman-Bradshaw,** Labcorp; **Vinnie Amendolare,** Novartis; **Sameh Azer,** Johnson & Johnson; **John Banovetz,** 3M; **Devavrat Bapat,** Johnson & Johnson; **Christina Bucci-Rechtweg,** Novartis; **Laurie Burns,** Johnson & Johnson; **Esther Campi,** Campi & Company; **Carla Cartwright,** Johnson & Johnson; **Brian Caveney,** Labcorp; **Raymond Chiu,** 3M; **C. Stephen Chukwurah,** National Academy of Medicine; **Isabel Gomes,** 3M; **Sarah Grant,** Novartis; **Paul Graves,** Johnson & Johnson; **Tracy Haller,** Novartis; **John Hoffman,** Johnson & Johnson; **Donald E. Horton, Jr.,** Labcorp; **Julie Khani,** American Clinical Laboratory Association; **Paul Kirchgraber,** Labcorp; **Jennifer Leeds,** Novartis; **Michele Mazur,** Labcorp; **Joe McGowan,** Novartis; **Amit Nastik,** Novartis; **Daniel T. O'Connor,** 3M; **John Pournoor,** 3M; **Naomi Rodiles,** 3M; **Jacob Rund,** Labcorp; **Anil Saggi,** Novartis; **Mark Schroeder,** Labcorp; **Louise Serio,** Reservoir Communications Group; **Oren Shur,** Johnson & Johnson; **Badhri Srinivasan,** Novartis; **Meghan Drenan Stone,** Johnson & Johnson; **Amy Summy,** Labcorp; and **Sandra van der Vaart,** Labcorp, for their valuable contributions to this paper.

This paper benefitted from the thoughtful input of **Adam Gluck,** Sanofi U.S.; **Tracy Lieu,** Kaiser Permanente; **Joshua Makower,** Stanford University; and **Pamela Tenaerts,** Medable, Inc.

Conflict-of-Interest Disclosures

Dr. Lewis-Hall discloses that she is a member of the board of directors for SpringWorks Therapeutics, Exact Sciences, and 1Life Healthcare; she is a consultant for PhRMA; and she is an advisor to SAAMA Technologies, Topography Health, and Catalio. Dr. Mammen discloses that his employer received funding from the US government to develop a COVID-19 vaccine; that his employer collaborated with BCG; that his employer's COVID-19 vaccine has received emergency use authorization in the US, European Union, and other countries; and that Johnson & Johnson is a multi-faceted company that has pharmaceutical, consumer, and medical devices businesses. Dr. Narasimhan discloses that his employer is currently undertaking an internal drug discovery program toward a pan-Coronavirus Mpro inhibitor; that his employer has an option and license agreement to develop, manufacture and commercialize two Molecular Partners' anti-COVID-19 DARPin® candidates; and that his employer has initial agreements with Pfizer-BioNTech and CureVac to manufacture their COVID-19 vaccines, and with Roche for the production of the API for Actemra/RoActemra®. Mr. Schechter discloses that his employer has performed COVID-19 diagnostic and antibody testing, supported COVID-19 clinical trials and study opportunities of potential treatments and vaccines with external sponsors, and worked with the U.S. Centers for Disease Control and Prevention to provide sequencing of samples of SARS-CoV-2 and that for these laboratory testing and drug development services, his employer has received reimbursement from various sources, including governmental agencies; and that in preparing the submitted work, Labcorp consulted with the American Clinical Laboratory Association, the national trade association representing leading clinical laboratories.

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