How VA Innovative Partnerships and Health Care Systems Can Respond to National Needs: NOSE Trial Example

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Background: At the onset of COVID-19, essential supplies were not obtainable from manufacturers. This caused patients and clinicians to have additional risk and exposure to COVID-19 in some settings and the wasting of critical materials when testing was unavailable in other settings.

Observations: The Veterans Health Administration (VHA) developed and enacted contingency plans for depleted supplies under both its First Mission—to care for veterans—and its Fourth Mission—to support the American health care system in times of crisis. A partnership among the VHA, US Food and Drug Administration, the National Institutes of Health, and America Makes addressed national shortages with the curation and development of designs, testing protocols, product evaluation, and product validation. VHA leveraged digital manufacturing to produce nasopharyngeal swabs onsite—3-dimensional-printed nasal swabs—and validate them to cover the gap between stockpile depletion and ramp up of traditional product manufacturing.

Conclusions: This effort involved close collaboration between innovators and researchers within the organization and alongside government, industry, and academic partners. We illustrate this collaborative concept here with a use case of nasal swabs to demonstrate successes and lessons learned that are shaping how the VHA in conjunction with government and industry partners can shepherd this new strategy for crisis preparedness.

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Traditional manufacturing concentrates capacity into a few discrete locations while applying *lean* and *just-in-time* philosophies to maximize profit during times of somewhat predictable supply and demand. This approach exposed nationwide vulnerabilities even during local crises, such as the United States saline shortages following closure of a single plant in Puerto Rico following Hurricane Maria in 2017.[1] Interruptions to the supply chain due to pandemic plant closure, weather, politics, or surge demand can cause immediate and lasting shortages. Nasal swabs were a clear example.

At the onset of COVID-19, 2 companies—Puritan in Guilford, Maine, and Copan in Italy—manufactured nearly all of the highly specialized nasopharyngeal (NP) swabs singled out by the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) to test patients for COVID-19. Demand for swabs skyrocketed as the virus spread, and they became unattainable. The lack of swabs meant patients went undiagnosed. Without knowing who was positive, people with symptoms and known contacts were presumed positive and quarantined, impacting isolated patients, the health care professionals treating them, and the entire US economy.

3-DIMENSIONAL PRINTING SOLUTIONS

Manufacturing NP swabs is not trivial. Their simple shape conceals complexity and requires highly specialized equipment. The lead time for one non-US machine manufacturer was > 6 months at the start of the pandemic.

Digital manufacturing/3-dimensional (3D) printing represented a potential solution to the supply chain crisis.[2] Designers created digital blueprints for 3D-printed goods, face masks, face shields, and ventilator splitters were rapidly created and shared.[3,4] Scrambling to fill the critical need for NP swabs, many hospitals, businesses, and academic centers began 3D printing swabs. This effort was spearheaded by University of South Florida (USF) and Northwell Health researchers and clinicians, who designed and tested a 3D-printed NP swab from photocurable resin that was printable on 2 models of Formlabs printers.[5] Several other 3D-printed NP swab designs soon followed. This innovation and problem-solving renaissance faced several challenges well known to traditional manufacturers of regulated products but novel to newcomers.

The first challlenge was that these NP swabs predate FDA oversight of medical device development and manufacturing and no testing standards existed. Designers began casting prototypes out without guidance about the critical features and clinical functions required. Many of these designs did not have a clinical evaluation pathway to test safety and efficacy.

The second challlenge was that these swabs were being produced by facilities not registered with the FDA. This raised concerns about the quality of unlisted medical products developed and manufactured at novel facilities.

The third challenge was that small-scale novel approaches may offset local shortages but could not address national needs. The self-organized infrastructure for this crisis was ad hoc, local, and lacked coordinated federal support. This led to rolling shortages of these materials for years.

TABLE Design Inputs for Nasopharyngeal Swabs and 8 Standard Test Protocols to Evaluate Key Functions

Design input	Verification tests
Sterilizable	Third-party sterilization validation
Fit nasal cavity and reach the sampling location	Go/no-go gauge
Should not substantially increase risk of nose bleeds vs standard of care	Abrasion protocol
Should not break in nasal cavity	Go/no-go gauge; fatigue bending protocol
Must collect and release sufficient COVID-19 sample for valid test result	Adsorption protocol; elution protocol
Compatible with/fit within transportation tube	Breakpoint function test
Material must not interfere with polymerase chain reaction results	Polymerase chain reaction interference protocol
Material must prove safe for mucus membrane contact	Material biocompatibility analysis

Two studies were performed early in the pandemic. The first study evaluated 4 prototypes of different manufacturer designs, finding excellent concordance among them and their control swab.[6] A second study demonstrated the USF swab to be noninferior to the standard of care.[7] Both studies acknowledged and addressed the first challenge for their designs.

COLLABORATIONS

Interagency

Before the pandemic, the US Department of Veterans Affairs (VA) had been coordinating with the FDA, the National Institutes of Health (NIH), and the nonprofit America Makes to bring medical product development and manufacturing closer to the point of care.

At the outset of the COVID-19 pandemic, the collaboration was formalized to address new challenges.[8] The objectives of this collaboration were the following: (1) host a digital repository for 3D-printed digital designs for personal protectice equipment and other medical supplies in or at risk of shortage; (2) provide scientifically based ratings for designs according to clinical and field testing; and (3) offer education to health care workers and the public about the digital manufacturing of medical goods and devices.[4,9]

A key output of this collaboration was the COVID 3D Trusted Repository For Users And Suppliers Through Testing (COVID 3D TRUST), a curated archive of designs. In most cases, existing FDA standards and guidance formed the basis of testing strategies with deviations due to limited access to traditional testing facilities and reagents.

To address novel NP swabs, working with its COVID 3D TRUST partners, the VA gathered a combined list of clinical- and engineering-informed customer requirements and performed a hazard analysis. The result was a list of design inputs for NP swabs and 8 standard test protocols to evaluate key functions (Table).[10] These protocols are meant to benchmark novel 3D-printed swabs against the key functions of established, traditionally manufactured swabs, which have a long record of safety and efficacy. The protocols, developed by the VA and undergoing validation by the US Army, empower and inform consumers and provide performance metrics to swab designers and manufacturers. The testing protocols and preliminary test results developed by the VA are publicly available at the NIH.[11]

Intra-agency

The use of the inputs and verification tests noted in the Table may reduce the risk of poor design but were inadequate to evaluate the clinical safety and efficacy of novel swabs. Recognizing this, the VA Office of Healthcare Innovation and Learning (OHIL) and the Office of Research and Development (ORD) launched the Nasal Swab Objective and Statistical Evaluation (NOSE) study to formally evaluate the safety and efficacy of 3D-printed swabs in the field. This multisite clinical study was a close collaboration between the OHIL and ORD. The OHIL provided the quality system and manufacturing oversight and delivery of the swabs, and the ORD provided scientific review, research infrastructure, human subjects oversight, administrative support, and funding and fiscal oversight. The OHIL/ORD collaboration resulted in the successful completion of the NOSE study.

This study (manuscript under preparation) yielded two 3D-printing production processes and swab designs that had comparable performance to the standard of care, were manufacturable compliant with FDA guidelines, and could be produced at scale in a distributed manner. This approach directly addressed the 3 challenges described earlier.

LESSONS LEARNED

Swabs were an example of supply challenges in the pandemic, but advanced manufacturing (notably, digital designs leading to 3D-printed solutions) also served as a temporary solution to device and product shortages during the COVID-19 pandemic. Digital designs and 3D printing as manufacturing techniques have the following key advantages: (1) they are distributed in nature, both in the breadth of locations that have access to these manufacturing platforms and in the depth of material choice that can be used to fabricate products, which alleviates the threat of a disaster impacting manufacturing capacity or a material stream; (2) they do not require retooling of machinery so new products can deploy rapidly and on demand; and (3) the speed of digital iteration, printing, and revision allows for rapid product development and production.

There also are notable disadvantages to these techniques. First, because 3D printing is a newer technology, there is less general depth of knowledge regarding design and material choice for additive manufacturing. Second, the flexibility of 3D printing means that operators must increase awareness of the factors that might cause the fabrication of a part to fail in either printing or postprocessing. Third, there are significant gaps in understanding how materials and manufacturing processes will perform in high-stakes settings such as health care, where performance and biocompatibility may be critical to support life-sustaining functions. Fourth, digital files are vulnerable to intentional or unintentional alteration. These alterations might weaken design integrity and be imperceptible to the manufacturer or end user. This is a prevalent challenge in all open-source designs.

The pandemic materialized quickly and created vast supply chain challenges. To address this crisis, it was clear that the average 17-year interval between research and translation in the US was unacceptable. The VA was able to accelerate swiftly many existing processes to meet this need, build new capabilities, and establish new practices for the rapid evaluation and deployment of health care products and guidance. This agile and innovative cooperation was critical in the success of the VA's national support for pandemic solutions.

Finally, although COVID 3D TRUST was able to provide testing of submitted designs, this collaboration was not a substitute for the "peacetime" process of manufacturing site registration with the FDA and product listing. COVID 3D TRUST could evaluate designs only, not the production process, safety, and efficacy.

CALLS TO ACTION

The pandemic's impact on medical supply chain security persists, as does the need for greater foresight and crisis preparation. We must act now to avoid experiencing again the magnitude of fatalities (civilian and veteran) and the devastation to the US economy and livelihoods that occurred during this single biological event. To this end, creating a digital stockpile of federally curated, crisis-ready designs for as-needed distribution across our US industrial base would offer a second line of defense against life-threatening supply chain interruptions. The realization of such a digital stockpile requires calls to action among multiple contributors.

Collaborations

The VA's Fourth Mission is to improve the nation's preparedness for response to war, terrorism, national emergencies, and natural disasters. The VA does this by developing plans and taking actions to ensure continued service to veterans, as well as to support national, state, and local emergency management, public health, safety, and homeland security efforts.

The VA partnership with the FDA and NIH during the pandemic enabled successful coordination among federal agencies. Numerous other agencies, including the US Department of Defense (DoD), the Biomedical Advanced Research and Development Authority (BARDA), and the Defense Advanced Research Projects Agency (DARPA), also developed and executed successful initiatives.[12-14] The joint awareness and management of these efforts, however, could be strengthened through more formal agreements and processes in peacetime. The VA/FDA/NIH Memorandum of Understanding is a prototype example of each agency lending its subject matter expertise to address a host of pandemic challenges collectively, cooperatively, and efficiently.[8]

Public-private partnerships (eg, VA/FDA/NIH and America Makes) led to coordinated responses for crisis readiness. The Advanced Manufacturing Crisis Product Response Program, a multipartner collaboration that included VA, addressed 7 crisis scenarios, 3 of which

were specifically related to COVID-19.[15] In addition, both BARDA and DARPA had successful public-private collaborations, and the DoD supported national logistics and other efforts.[12-14] Clearly, industry and government both recognize complementary synergies: (1) the depth of resources of US industry; and (2) the national resources, coordination, and clinical insight available through federal agencies that can address the challenges of future crises quickly and efficiently.

When traditional supply chains and manufacturing processes failed during the pandemic, new techniques were exploited to fill the unmet material needs. Novel techniques and product pathways, however, are untested or undeveloped. The collaboration between the ORD and OHIL in support of NP swab testing and production is an example of bringing research insight, regulated product development, and manufacturing together to support a complete product life cycle.

Joint Awareness and Management

The VA continues to refine the joint awareness and management (JAM) process of products from ideation to translation, to shorten the time from research to product delivery. JAM is a VA collaborative committee of partners from ORD research offices and technology transfer program, and the OHIL Office of Advanced Manufacturing, which seeks additional support and guidance from VHA clinical service lines, VA Office of General Council, and VA Office of Acquisitions, Logistics, and Construction.

This team enables the rapid identification of unmet veteran health care product needs. In addition, JAM leverages the resources of each group to support products from problem identification to solution ideation, regulated development, production, and delivery into clinical service lines. While the concept of JAM arose to meet the crisis needs of the pandemic, it persists in delivering advanced health care solutions to veterans.

A Proposed Plan

The next national crisis is likely to involve and threaten national health care security. We propose that federal agencies be brought together to form a federally supported digital stockpile. This digital stockpile must encompass, at minimum, the following features: (1) preservation of novel, scalable medical supplies and products generated during the COVID-19 pandemic, to avoid the loss of this work; (2) clinical maturation of those existing supplies and products to refine their features and functions under the guidance of clinical, regulatory, and manufacturing experts—and validate those outputs with clinical evidence; (3) manufacturing maturation of those existing supplies and products, such that complete design and production processes are developed with the intent to distribute to multiple public manufacturers during the next crisis; (4) a call for new designs/intake portal for new designs to be matured and curated as vulnerabilities are identified; (5) supply chain crisis drills executed to test public-private preparedness to ensure design transfer is turnkey and can be engaged quickly during the next crisis; and (6) public-private engagement to develop strategy, scenarios, and policy to ensure that when supply chains next fail, additional surge capacity can be quickly added to protect American lives and health care, and that when supply chains resume, surge capacity can be redirected or stood down to protect the competitive markets.

This digital stockpile can complement and be part of the Strategic National Stockpile. Whereas the Strategic National Stockpile is a reserve of physical products that may offset product shortages, the digital stockpile is a reserve of turnkey, transferable designs that may offset supply chain disruptions and production-capacity shortages.

CONCLUSIONS

The success of 3D-printed NP swabs is a specific example of the importance of collaborations across industry, government, innovators, and researchers. More important than a sole product, however, these collaborations demonstrated the potential for game-changing approaches to how public-private partnerships support the continuity of health care operations nationally and prevent the potential for unnecessary loss of life due to capacity and supply chain disruptions.

As the largest health care system in the US, the VA has a unique capability to lead in the assessment of other novel 3D-printed medical devices in partnership with the FDA. The VA has a unique patient-centered perspective on medical device efficacy, and as a government institution, it is a trusted independent source for medical device evaluation. The VA's role in the evaluation of 3D-printed medical devices will benefit veterans and their families, clinicians, hospitals, and the broader public by providing a gold-standard evaluation for the growing medical 3D-printing industry to follow. By creating new pathways and expectations for how federal agencies maintain crisis preparedness—such as establishing a digital stockpile—we can be equipped to serve the US health care system and minimize the effects of supply chain disruptions.

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