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Zero In on Pandemic Prevention

With a smaller budget than hoped for, ARPA-H must focus. Here's how the new agency can synergize existing government efforts and advance breakthrough technologies that protect us all.

More than 20 years ago, Robert Cook-Deegan asked in this magazine, "Does NIH Need a DARPA?" The article described the innovation funding model pioneered by the Defense Advanced Research Project Agency—created during the space race to stay ahead of the Soviet Union—and posited that a similar funding mechanism housed within the National Institutes of Health could garner breakthroughs in health. Since then, DARPA-like government agencies have been created for homeland security, intelligence, and energy technologies, for example, with variable success. Now, the "ARPA for health" concept has resurged. More than a year before he became a presidential nominee, Joe Biden spoke of creating a new federal agency that could pursue health breakthroughs beyond current, narrower government functions. Last year, the Advanced Research Projects Agency for Health (ARPA-H) finally launched with an initial $1 billion budget.

ARPA-H's mandate for broad transformations distinguishes it from NIH efforts, which tend to specialize in specific disease areas or disciplines. Aiming to solve real-world health problems by pushing the boundaries of science and technology, ARPA-H has only a fraction of DARPA's annual budget, which may force its early ambitions to be more modest. Still, inaugural director Renee Wegrzyn and her team are emphasizing broad tools and platforms, seeking solutions that are "disease agnostic."

We are a technologist and physician team that contributed to the Bipartisan Commission on Biodefense's "Apollo Report," a proposal for how technological innovation could end pandemic threats by 2030. When ARPA-H laid out four priority areas in its request for research proposals earlier this year, we saw opportunities for projects that advance the agency's aims and could also help make pandemics a horror of the past.

We spoke with more than 20 experts from government, academia, and industry to vet the idea: Could ARPA-H achieve the broad transformations it aspires to by pursuing the particular ambition of eliminating pandemics? They agreed that by focusing on the grand challenge of pandemic prevention, ARPA-H could develop breakthrough technologies that fit its ambitious goals, integrate across health systems, become part of day-to-day life, and—yes—forestall both pandemics and common infectious diseases. What's more, by pursuing projects that no other agency could be expected to take on, ARPA-H could also link up existing problem-analysis and research capacities that are currently spread across the government.

Transforming health—for all

The vision of eliminating pandemics fits well with ARPA-H's unique take on the DARPA model. In the 1970s, DARPA's then director George Heilmeier developed a set of surprisingly straightforward questions that have come to be known as the Heilmeier Catechism. The questions continue

to serve as guiding principles to help determine which technical risks are worth taking. They demand program managers "articulate [their] objectives using absolutely no jargon" and ask, "Who cares? If you are successful, what difference will it make?" To these questions, ARPA-H has added others. One of these gets at the heart of its mission: "To ensure equitable access to all people, how will cost, accessibility, and user experience be addressed?"

Pandemics spread inequity as much as they spread sickness. COVID-19 pushed tens of millions into poverty. Those with the lowest incomes have had the largest financial losses, per data from the World Bank. Even in the richest countries, people living in poorer communities, who often live in multigenerational homes and cannot work remotely, were more vulnerable to the disease. In cities like New York, Latino and Black populations were twice as likely to die from COVID-19 as white populations. Future infectious diseases are also likely to disproportionately affect those with lower socioeconomic status or living in the global South—just as COVID-19 did. Technologies to prevent pandemics may be one of the best ways ARPA-H could tackle systemic health inequities.

Strategic convergence

Alongside the Heilmeier questions, ARPA-H set out four overarching priorities: building broad tools, making scalable solutions that increase access and affordability, proactively improving personal health, and creating resilient systems that can withstand disruption. Each of these general goals dovetails nicely with advances—technological, medical, and social—that would help prevent future pandemics.

Instead of specific programs targeting single diseases, ARPA-H's first priority is to seek tools that tackle multiple ills at once. Of the tools that prevent pandemics, several already exist: indoor toilets, water treatment, and pasteurization. Although these are all taken for granted as features of modern life, they should be understood as outbreak prevention technologies, stopping the spread of disease by food, water, and human contact without targeting any specific pathogen or even being explicitly considered an aspect of health care. Similarly, mRNA vaccines are another platform that can be redeployed for pathogen after pathogen.

Future platform technologies might include wearable sensors that detect infection noninvasively and before symptoms appear. This real-time monitoring could bring radical insights for quashing nascent outbreaks. Scientists have already prototyped sensors that detect intact viruses in breath and smartwatches that predict when their wearers have an infection based on sleep and heart rate patterns. Outbreak prevention might literally become part of a person's everyday wardrobe. Similarly, imagine genomic sequencers that could be placed alongside or inside smoke detectors to monitor pathogens in the air. Or maybe these could be further miniaturized and fit into toothbrush caps, turning daily hygiene routines into early infection alarm systems.

ARPA-H's second strategic goal aims to improve access and affordability while addressing systemic challenges "at a scale that reaches every citizen, regardless of geography or resources." This is important in health because many of the latest health advances are financially or otherwise out of reach for the average American—let alone marginalized or rural communities.

Investments in pandemic prevention today could reduce the health disparities of tomorrow. For example, self-administered intranasal vaccines and microneedle patches wouldn't require time off work, online scheduling, or travel to a clinic or pharmacy. Every household, including rural ones, could get vaccines in the mail to administer at home. Other innovations might include portable vaccine "printers" that manufacture vaccines when and where they are needed, eliminating complex supply chain logistics.

ARPA-H's third goal, proactive health, has been described by Wegrzyn as "keeping people from becoming patients in the first place." That spans new health equipment, buildings that promote health and safety, innovative behaviors and social conventions, and artificial intelligence tools that mitigate human error in medical care. One expert envisioned that "ARPA-H could create capabilities that foster a cultural change toward a public health system that empowers researchers, policymakers, and the American population to make evidence-based decisions."

A concrete example of equipment would be self-sterilizing, easy-to-wear, inexpensive personal protective equipment. Creating protective wear that is functional, comfortable, and perhaps even fashionable would not only prevent pathogen transmission—it could conceivably boost health by eliminating environmental pollutants, quieting allergies, and reducing asthma attacks. Other technology opportunities are in infrastructure: "immune systems" for buildings that use fast filtration or safe germicidal lighting to block airborne transmission indoors and allow school and other community functions to remain safely open. These would pay off even without a pandemic by reducing rates of influenza, the common cold, and more. Productivity and other losses from infectious diseases in the United States has been estimated at well over $100 billion a year, with a large portion stemming from respiratory pathogens.

The final goal is to build stronger, more stable systems, which Wegrzyn characterizes as "the things we can integrate to help us be resilient against the next pandemic." As hospitals filled with COVID-19 cases, disrupted cancer treatments raised the risk of death, canceled surgeries increased mortality, and life-saving catheterizations to treat heart attacks were delayed. Patients who already had limited access to health care were even less likely to receive treatment.

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Systems-level technologies for governments and public health departments could boost resilience by supporting informed decisions and adaptive responses for unplanned surges in demand. Think software that draws on data such as traffic patterns, Google searches, wastewater monitoring, and hospital capacity so that nurses, medicines, and more can be sent to facilities before supplies run out or staffing shortages stall treatments.

New technologies could help overhaul health care conventions that have become tragically counterproductive. Clustering infectious patients in a hospital with other sick—and often immunocompromised—patients is far from ideal. With remote monitoring and portable labs, home-based care could once again be the standard for quarantined patients.

These ARPA-H priorities are not simply aligned with efforts to prevent pandemics; such efforts offer a proof of concept for ARPA-H's pitch for the utility of going beyond finding bespoke molecular therapies for specific diseases. Also needed are innovations to counter systemic, geographical, cultural, and nonmonetizable contributors to ill health—exactly the sort of approach ARPA-H could pioneer.

Synergizing, not duplicating

Pandemic prevention at ARPA-H need not come at the expense of other pandemic preparedness efforts. ARPA-H has explicitly stated that its remit is for projects "that cannot otherwise be pursued within the health funding ecosystem due to the nature of the technical risk." ARPA-H plans to pursue its own category of effort with revolutionary or unconventional approaches that other agencies would avoid as too likely to fail because of their complexity or untested hypotheses. In other words, to win ARPA-H support, technologies cannot be incremental improvements or something other agencies would take on.

While several other US agencies are charged with preventing pandemics, all have more focused missions. For example, the White House recently launched Project Next Gen, a follow-up to Operation Warp Speed that aims to develop pan-coronavirus vaccines and therapeutic antibodies. This is a laudable endeavor. Yet there is more work to do since a pan-coronavirus vaccine will offer immunity against just a fraction of the over 200 viruses known to cause common colds. ARPA-H's disease-agnostic mandate could prevent exposure to a much broader swath of pathogens and combine approaches from disciplines beyond the biomedical sciences.

ARPA-H can complement pandemic-related efforts of agencies across the government without duplicating them. The Centers for Disease Control and Prevention applies its epidemiological expertise to understand disease spread and to pursue and evaluate epidemiological interventions, but is not well set up to adopt unexpected, engineering-led approaches from other disciplines. Similarly, the Biomedical Advanced Research and Development Authority (BARDA) is charged with having an array of medical countermeasures at the ready—which it does superbly—but funding vaccines, therapeutics, and diagnostics against accidents and attacks leaves BARDA little scope to take on the technical risk of an ARPA. BARDA DRIVe, a division within BARDA, aims to stimulate innovation using flexible funding and public-private partnerships, but its overall budget is at the very most the size of two ARPA-H programs, limiting its ability to make large, ambitious technical bets. The DARPA Biological Technologies Office pursues all sorts of biological innovations potentially useful to the Department of Defense, but many, such as biofuels, fall outside medical applications, and the office does not prioritize nonbiological technologies, such as air sterilization, that could be used to fight infectious disease. NIH supports research projects designed by independent investigators and selected by peer review. Its pandemic efforts will be invaluable in characterizing pathogens and in advancing infrastructure for drug and diagnostic testing. What's more, NIH does contain efforts such as the Center for Advancing Translational Sciences and Centers for Accelerated Innovations, which study the science of and develop best practices in translation of discovery into products, efforts ARPA-H can draw on for its own product-specific translation efforts. Still, when it comes to supporting commercialization and translation, NIH's resources and methods are very different from the risky, top-down efforts ARPA-H can pursue.

All of these agencies are doing essential work in producing knowledge and analyzing problems around pandemics. ARPA-H presents an opportunity to amplify and perhaps even cross-pollinate efforts across different agencies.

Bringing health home

Creating an ARPA offers opportunities for transformative breakthroughs—but does not guarantee them. Some clones, such as ARPA-E (for energy) or IARPA (for intelligence), have positive track records. Others, such as the Homeland Security

ARPA, have been less successful in transitioning technologies from research scale to useful deployment. ARPA-H is making steps toward revamping the general model of tech transition. A focus on pandemics could help bridge stubborn gaps in bringing pandemic prevention technologies to market.

One expert told us that "true innovation will require innovation in transition models, too," meaning technical innovation alone is insufficient. For example, one big challenge will be figuring out how to "pull" prototypes out into society and the marketplace, a challenge likely to require innovations in economics and policy. Transitioning a technology into actual use generally relies on a promising market for the technology (a *demand pull*). While DARPA has a clear, deep-pocketed customer with the Department of Defense, there is no obvious counterpart for ARPA-H. That means many technologies nurtured by ARPA-H will eventually require both private investors and customers to move products from research, to development, and finally to deployment. ARPA-H has already signaled its attention to this transition by creating a dedicated office, the Project Accelerator Transition Innovation Office (PATIO).

ARPA-H has already announced plans to pursue. Deploying nuanced contracting could allow rapid procurement and technology certification, which will enable a rapid response to an emerging outbreak. For other innovations such as software and infrastructure, ARPA-H may well need to work with yet more departments.

Anticipating risks

Being at the forefront of technology has also meant that ARPAs have been at the cutting edge of other types of risks aside from technical risk (which well-designed programs can account for). In anticipation of a rapidly shifting risk landscape, ARPA-H has added a tenth question to the original list of Heilmeier questions. It asks program managers to consider: "How might this program be misperceived or misused (and how can we prevent that from happening)?"

There is probably no better training ground for mastering the art of predicting and mitigating these risks than pandemic preparation and prevention. A wealth of scholarship and experience has emerged around what drives acceptance for vaccines and other prevention measures.

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Here, ARPA-H can draw valuable lessons from its predecessor, ARPA-E. Like ARPA-H, it lacks a government customer with a procurement budget, which prompted ARPA-E to develop tailored strategies for technology transfer. ARPA-E employs tech-to-market advisors who help project teams move their products from the lab to the market, a transition where many medical advances get waylaid. For example, one diagnostics company filed for bankruptcy just days prior to finally receiving Food and Drug Administration (FDA) authorization for its combined COVID-19 and influenza diagnostic, which would have helped those who test negative for COVID-19 but actually have influenza know to isolate and take health precautions. ARPA-H's PATIO will provide support similar to ARPA-E's advisors via Partnership Intermediary Agreements, which will engage experts in academia and the private sector to pressure-test ideas with the end customer in mind.

ARPA-H also plans to closely interact with the Centers for Medicare & Medicaid Services and the FDA to streamline the regulatory process and to identify customers for its products. For example, in non-pandemic times, pandemic vaccines lack a guaranteed market. Prizes and advance market commitments are tools that could potentially create a market incentive. Another is flexible government contracting, which Academics, policymakers, and stakeholders all found themselves proactively engaging on these issues in the last three years. Collaborating with this expertise can help ARPA-H get to grips on this particular (and particularly important) issue and to gain practical experience with broader issues of misperception and misuse.

Unlike technical risk, in which a financial investment may fail to pay off, misperception and misuse risks are unrestrained in their potential damage—and thus crucial to anticipate. One expert told us, "The first step in solving a problem is thinking about it."

Pandemic prevention is a uniquely difficult and ambitious challenge that cannot be solved through traditional research or commercial activity alone. The technology required to achieve a pandemic-free future will be transformative—and is exactly the kind of technology that ARPAs are known for delivering. By taking big, ambitious bets now, ARPA-H can make the next pandemic become a matter of *if*, not *when*.

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