ARPA-H: Risky or Revolutionary? The Challenges and Opportunities of Biden's New Biomedical Research Agency

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Abstract: The acceleration of COVID-19 testing platforms and vaccine development has demonstrated the possibility of expediting research for similar biomedical breakthroughs. However, the National Institutes of Health (NIH) lacks a framework to regularly sustain this type of research. A new federal agency, the Advanced Research Projects Agency for Health (ARPA-H), offers a unique opportunity to capitalize on the lessons learned from the COVID-19 pandemic and drive federal investment into high-risk, high-reward biomedical research. ARPA-H will mirror the flat bureaucratic structure of the successful Defense Advanced Research Projects Agency (DARPA) through the employment of independent project managers. ARPA-H is also unique in how it centers equity in the agency's core mission. These unique traits could enable the agency to fill the gaps in current biomedical research under the NIH. Nonetheless, ARPA-H's implementation is not without challenges: its incorporation within the NIH has raised concerns regarding its ability to specialize in high-risk research and the diversion of funding away from the rest of the NIH. These worries can be mitigated through the separation of ARPA-H and the NIH. Successful implementation of the ARPA-H framework would supplement current NIH work, diversify the US federal research strategy, accelerate promising breakthroughs, promote equity in health, and transform the nature of biomedical research in the US.

I. Background

How were scientists able to make the COVID-19 vaccine within one year? Can we, as scientists, similarly accelerate other such breakthroughs for diseases like cancer, Alzheimer's, and diabetes? The first step the government has taken to capitalize and extrapolate from the lessons learned during COVID-19 onto future biomedical research is the establishment of the Advanced Research Projects Agency for Health (ARPA-H). ARPA-H offers a unique opportunity to advance high-risk, high-reward research typically underfunded in NIH's traditional focus on incremental, basic research. For ARPA-H to succeed, it must leverage lessons from the NIH's accelerated development of COVID-19 vaccines; receive guidance from existing advanced research project-based agencies such as the successful Defense Advanced Research Projects Agency (DARPA); and address the concerns of exacerbated health inequities during and post-pandemic into its core mission of funding transformative biomedical research.

The NIH has previously successfully managed large, user-focused research projects such as Rapid Acceleration of Diagnostics (RADx) and the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) programs. These initiatives required the NIH to do away with its usual risk aversion and fiscal and temporal constraints to combat the national COVID-19 emergency. This unconventionally aggressive approach paid off as the RADx program resulted in the creation of over thirty new COVID-19 testing technology platforms, while the ACTIV program not only developed the COVID-19 vaccines but also enhanced the existing mRNA platform to transform future vaccine development (Lee 2021). The NIH's results with these programs demonstrate the potential value of large, high-risk, entrepreneurial projects to society.

Yet despite the successes of these previous NIH programs, the NIH lacks the framework to regularly support such accelerated breakthroughs. In fact, after the 2003 SARS outbreak through the COVID-19 pandemic, researchers working on coronavirus vaccines, treatments, and diagnostics struggled to find funding from agencies like the NIH, which cited concerns such as irrelevance and low monetary returns (Lee 2021). The US spends nearly $178 billion or 20% of its non-defense discretionary budget on health (US Congressional Budget Office 2021). However, very little of that funding ends up tackling society-wide challenges through research and development (Prabhakar 2021). Instead, the NIH spends on foundational, curiosity-driven research with the expectation that industry utilizes the basic science to advance health through practical applications. While this strategy has enabled the NIH to begin addressing society-wide challenges that profit-driven companies would be hesitant to tackle due to the lack of significant return on investment, the expectation that industry would further their work through innovation has not been entirely met and leads to the severe underinvestment of enterprising, user-driven projects relative to their potential impact (Collins et al. 2021).

This is especially true concerning diseases that primarily affect marginalized populations. For example, a recent study comparing funding and outcomes between cystic fibrosis and sickle cell disease—both inheritable, debilitating conditions—reports that similar federal research funding is directed towards both disorders, even though sickle cell disease has thrice the prevalence of cystic fibrosis (Farooq et al. 2020). Demographically, sickle cell disease primarily afflicts those of African/Black descent while cystic fibrosis generally affects those of White descent. This disproportionate focus has subsequently translated to industry funding disparities as there have been twice as many pharmaceutical and drug development trials for cystic fibrosis than for sickle cell disease (Farooq et al. 2020). Thus, both industry and academia have shown to not adequately support research in the context of conditions that affect marginalized populations and projects that return seemingly a less significant return on investment.

A specialized agency that can absorb the costs and risks associated with the pursuit of unconventional ideas and provide for the coordination of research goals across industry, academia, and government is needed. Such an agency would not only strengthen the relationship between different stakeholders and promote entrepreneurship through funding user-focused healthcare technologies but would also contribute to the bridging of current funding gaps in marginalized communities. It is time for the US to streamline federal science and technology policy to foster advancement in biomedical research that is not purely profit-driven and develop a collaborative hub that can leverage the strengths of both public initiatives and private industry.

II. ARPA-H as a solution
ARPA-H provides such a framework for government investment in high-risk, high-reward biomedical research. Namely, the agency's bureaucratic structure and equity-centered mission would enable ARPA-H to pursue fast-tracked research projects that focus on a wide variety of diseases and health conditions, including those that disproportionately impact marginalized communities.

i. ARPA-H as a nimble organization

Modeled after the Defense Advanced Research Projects Agency (DARPA)—a federal agency credited with the creation of the Internet, GPS, self-driving cars, and mRNA vaccines—ARPA-H is designed to be a nimble organization with a flat bureaucratic structure composed of (eventually) one hundred project managers who report directly to the agency director (Cook-Deegan 1997). These project managers must be recruited similarly to the DARPA model: from industry and top research universities, selected for their bold ideas, and given funding autonomy and flexibility in the projects they pursue and evaluated under a time-bound, metric-driven system that incentivizes bold ideas and normalizes failures (Lee 2021). Under this model, the agency project managers will identify investable projects rather than relying on NIH's peer review system, which has suffered from historical conservatism that stifles innovative proposals, inconsistency between peer reviewers, and biases in project selection (Savage and Simpson 2021). Instead of being scored or ranked, the proposals should follow a similar pattern utilized by DARPA in which they are simply evaluated by government experts on a boolean basis selected against specified evaluation criteria. This form of selectability determination will allow

researchers to conduct their research instead of spending their time and energy on writing long proposals, thus reducing the external costs for applicants and increasing transparency in the grant funding process (Cook-Deegan 1997).

ii. ARPA-H's emphasis on equity

ARPA-H emphasizes equity and inclusion in healthcare access and outcomes in its core mission—historically overlooked by federal research agencies—enabling it to tackle the root causes of health issues. Without interweaving a focus on disparities in research innovations and technological development, effective interventions would fail to reach those most in need, not only perpetuating but also exacerbating existing health inequities (Savage and Simpson 2021). ARPA-H specifically corrects this through funding projects focused on health equity—a stark departure from the NIH's track record: for example, during the COVID-19 pandemic, NIH-backed research programs struggled to involve marginalized populations and community stakeholders early in the research process. This was linked to the underrepresentation of Black, Indigenous, and People of Color (BIPOC) in clinical vaccine trials and heightened vaccine hesitancy. This can be attributed to the difficulty in prioritizing community engagement and stakeholder involvement in the current NIH grant application process for human participants-based research (Grumbach et al. 2021). The NIH's grant funding process itself is also subject to systemic racial biases. Black Principal Investigators (PIs) are less likely to receive approval for grant funding than White PIs (Taffe and Gilpin 2021). The NIH has yet to make up for the racial disparities in grant funding through the inclusion of equity initiatives in the federal grant funding process.

ARPA-H must aim to remediate these failures of the NIH through broadening participation in the research ideation process. More specifically, the agency should plan on engaging key stakeholders and the research's end-users (e.g., patients, clinicians, targeted marginalized populations) and prioritizing research projects that solve community health challenges. At the organizational level, ARPA-H plans on recruiting leaders and project managers from diverse disciplinary and demographic backgrounds to promote an atmosphere free of barriers to collaboration and inclusion. However, organizations such as the NIH have also recently implemented similar plans with rather mixed results (Britt 2020). In order to succeed, these initiatives will require proper implementation through interweaving an equity-centered approach in all of the agency's projects. Such emphasis and proper implementation of diversity plans would not only counter systemic racial biases in federal grant funding but also contribute to the agency's mission to foster creativity and an entrepreneurial spirit through the synergistic utilization of the strengths and experiences of various agency leaders and project managers (Swartz et al. 2019).

III. Challenges and policy suggestions
The implementation of ARPA-H is not without challenges, however. Many of these challenges can be anticipated and renegotiated with available resources. The major challenges to the successful implementation of ARPA-H and their potential resolutions are discussed below.

i. ARPA-H's mission and the role of program managers

Some critics such as Anna Goldstein, a researcher on the analogous Advanced Research Projects Agency for Energy (ARPA-E), argue that ARPA-H's mission is too broad and would be better focused on neglected diseases that receive less funding from other sources (Tollefson 2021). Francis Collins, President Biden's chief scientific advisor and former NIH Director, however, recently stated that ARPA-H will not ignore any disease and it is precisely ARPA-H's broad mission that enables its network of program managers significant intellectual freedom in prioritizing what research to pursue (Kaiser 2021). Nonetheless, this criticism underscores how vital program managers are, as they form the backbone of the ARPA model. Risk-averse or irresponsible project managers could work against the agency's bold mission and accountability needed for the ARPA-H mission to succeed. To avoid this, the ARPA model must adopt DARPA's inbuilt turnover system that limits the term of project managers to 3-5 years. This would require project managers to work on endeavors under a significant time constraint that promotes a culture of boldness and swift results, while simultaneously allowing for

fast replenishment of ideas and the mitigation of stagnation.

ii. Navigating a complex healthcare environment

While ARPA-H's operating structure will resemble that of DARPA, it will have a fundamentally different mission than DARPA—biomedical research examines complicated biological systems in multiple contexts (patients, providers, hospitals, biopharmaceutical companies, etc.), while DARPA focuses on engineered systems for one end-user: the Department of Defense (DOD) (Collins 2021). ARPA-H's translational research and systems cannot exist in relative isolation from pertinent human behavior and social factors. The incorporation of community stakeholders in the entire research and design (R&D) lifecycle will allow for ARPA-H to approach complex health issues holistically. Furthermore, ARPA-H will be tasked to navigate the complex biomedical regulatory environment and then advance any novel medical intervention in the highly competitive marketplace of the US healthcare system. Therefore, ARPA-H cannot rely entirely on DARPA as a blueprint and will likely need to work collaboratively with experts from federal agencies embedded within the healthcare ecosystem such as the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA). With such a framework, ARPA-H can serve as a hub for collaboration, mutual understanding, and scientific advancement between users (e.g., patients, providers, hospitals); translational researchers from the pharmaceutical industry and biotech startups or firms; and large regulatory agencies, thus expanding the current scope of government agencies in modern healthcare.

iii. ARPA-H's relationship with the NIH and the Department of Health and Human Services (HHS)

Another major point of contention for lawmakers is whether to establish ARPA-H within the NIH or as an independent agency under the HHS (Peterson 2022). Currently, a sort of compromise was reached with this decision: ARPA-H will be housed within the NIH but the agency director will report directly to the Secretary of Health and Human Services (Kaiser 2021).

Proponents of this settlement—including the Biden administration—have pointed to the short-term benefits of setting up ARPA-H within the NIH (Tollefson 2021). For one, this move would allow for ARPA-H to start hiring and awarding contracts relatively quickly as it can utilize the administrative resources of the NIH such as human resources, payroll, and legal services. This would invariably decrease the agency's administrative costs and increase the ease of sharing expertise and knowledge between the two agencies. Furthermore, the risk of unproductive or even rival duplication of biomedical research decreases through this organizational structure.

Nonetheless, housing ARPA-H within the NIH raises important concerns, namely that a lack of total autonomy might limit the agency's ability to operate beyond the NIH's culture of conservatism (Kaiser 2021). This runs the risk of turning ARPA-H into simply another NIH institute that lacks its unique culture and approaches—things that are particularly needed if ARPA-H is to fulfill its role as a nimble, equity-focused agency. To mitigate the influence of the NIH on ARPA-H, lawmakers have decided to physically locate the ARPA-H headquarters away from the NIH main campus in Bethesda, Maryland (Peterson 2022).

Many lawmakers are unconvinced that the physical separation of the NIH and ARPA-H is enough to curb NIH's cultural influence on ARPA-H. Due to this, lawmakers are still pushing the "ARPA-H Act" in Congress to authorize the agency in the HHS. The House of Representatives recently passed the act, placing them in direct conflict with the current situation and the Biden administration's preference (Hunt and Wagner 2022a).

However, the authorization of ARPA-H through HHS also presents new problems. While this would increase ARPA-H's cultural autonomy, it also brings in added questions about the agency's accountability. Recently, the Biomedical Advanced Research and Development Authority (BARDA)—housed independently within the HHS—was found misusing millions of dollars of funding granted for vital vaccine research and pandemic preparedness on activities such as removing office furniture and news subscriptions (Stolberg 2021). Without sufficient oversight and

competent leadership, ARPA-H, too, could find itself with an irresponsible leader that might hamper the agency from realizing its goals. Thus, for ARPA-H to succeed, a strong, accountable director with an extensive track record must be appointed. The Biden administration can achieve such an appointment by choosing a leader with previous experience working in a biomedical division of an advanced research agency; broad entrepreneurial experience in industry and academia; and a strong commitment to systems-thinking and diversity and equity initiatives. A director with successful experience can be trusted to understand ARPA-H's mission and run the agency in the right direction.

iv. Competing funds with the NIH

The establishment of ARPA-H within the NIH has already brought it into competition with the NIH for federal funding. During the Fiscal Year (FY) 2022 hearings on budget requests, the Biden administration's budget requests for the NIH were dominated by budget requests for ARPA-H (Peterson 2022). Placing ARPA-H within the NIH has come at the expense of the NIH as it allows for the diversion of funding and federal attention away from the investment in basic research of the NIH (Serebrov 2022). House Appropriations Committee Chair Rosa DeLauro expressed her concern with the mere $274 million budget increase for the rest of the NIH in comparison to the $1 billion funding appropriated for the establishment of ARPA-H ("Washington Update" 2022). The president's FY 2023 budget request proposes a $4 billion (400%) increase for ARPA-H in the omnibus while flatlining NIH funding with a $275 million (0.6%) increase in comparison to FY 2022 spending levels (Hunt and Wagner 2022b). Rep. DeLauro and others across the aisle including Rep. Tom Cole feel as if the minimal budget increases for the NIH would be insufficient and threaten the progress made by sustained investment in basic biomedical research. Without adequate government funding, conducting basic research would not be sustainable as profit-driven corporations would continue to prioritize user-centered research. Subsequently, future innovation which relies on today's backbone of basic research would be adversely affected. Thus, competing funding between ARPA-H and NIH is a major issue in need of immediate remediation.

IV. Discussion
Despite the challenges discussed, the establishment and continued Congressional support of ARPA-H is very much needed. The success of NIH's RADx and ACTIV programs demonstrate the utility of high-risk, high-reward projects. The NIH's inability to continually implement and sustain these forms of expedited, user-focused projects due to the very nature of the research it supports—basic and incremental—combined with its rather limited focus on equity demonstrates the need for an agency like ARPA-H. However, while ARPA-H provides a framework to fulfill the gaps in our current federal approach to biomedical research, a few concerns need to be immediately addressed as the federal government begins the establishment of this agency. Firstly, Congress must codify a process for the selection of project managers—the backbone of this agency structure—from diverse demographic and academic backgrounds to promote a culture of creativity and equity. Furthermore, despite the Biden administration's expressed preference, Congress should act to establish ARPA-H separate from the NIH. This would enable the agency cultural autonomy from the NIH's relative risk-averse and conservative approach to research and mitigate concerns that ARPA-H will continue to dominate appropriation discussions for NIH funding. Thus, separating the two agencies should be a top federal priority. Lastly, selecting an experienced leader with public trust and relevant expertise by the Biden administration who can ensure agency accountability and mission execution should remain a top priority.

Even with such a leader, implementing ARPA-H will be challenging. Nonetheless, the opportunities ARPA-H offers far outweigh the challenges it presents in implementation. An ARPA-H-like system is necessary to supplement existing NIH practices and diversify the US's research strategy. Congress must continue to support ARPA-H and push for its establishment as a separate entity from the NIH. Doing so would accelerate promising breakthroughs, promote equity in health outcomes, and ultimately, transform the biomedical research ecosystem in the US.

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