Innovative Genomics Institute

Re: ARPA-H Request for Information – Design and Development of the ARPA-H ELSI Initiative

October 30, 2023

Attn: ARPA-H ELSI Program Team

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Dear ARPA-H ELSI Program Team,

The Innovative Genomics Institute (IGI), a public, academic research institute formed through a partnership between the University of California, Berkeley and the University of California, San Francisco, is pleased to submit comments in response to the Request for Information on the Design and Development of the ARPA-H ELSI Initiative.

Given the IGI's research focus on genome-editing technologies and their applications in human health, sustainable agriculture, and mitigating climate change, our response centers around the ethical, legal, and social considerations in the genetic therapies space. We hope the agency will find our suggestions helpful in this as well as other areas of research, development, and implementation.

We commend ARPA-H's leadership on prioritizing the ethical, legal, and social implications of the breakthrough health research the agency will fund and look forward to seeing how it will ensure that the benefits reaped from its taxpayer-funded investments reach everyone.

We hope the agency finds the below comments useful in the implementation of its ELSI Initiative and we stand ready to provide additional information or answer any questions as needed.

Affordability and access are key challenges with genetic therapies that will widen the health equity gap. We strongly encourage ARPA-H to fund innovative programs and activities that aim to improve access throughout the research and healthcare ecosystem.

Since the first FDA approval of genetic therapies (i.e., gene addition, genome-editing, and genetically modified cellular therapies) in 2017, there has been a steady stream of approvals that promises transformative patient outcomes. By providing a bespoke treatment to the underlying genetic defect or molecular driver of disease, and being inherently "platformizable", genome-editing therapies can provide interventions that millions of rare disease patients have been desperately waiting for. While scientifically feasible, the true challenges will lie in properly scaling development and streamlining review processes, making prices affordable, and ensuring equitable access to these breakthroughs.

Most factors contributing to access challenges are downstream in product development. The dire consequences that a lack of ethical, legal, and social considerations across the healthcare system is having on underprivileged and underserved populations will only be exacerbated if they remain

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unaddressed for genetic therapies. We recently concluded a yearlong deliberative effort, convening 30 multi-disciplinary experts, that explored some of these pressure points and potential solutions. This exercise highlighted to us three key areas where ARPA-H investment could be revolutionary:

1. Requiring access provisions in licensing agreements. With ARPA-H as a catapult for scientific leaps that will lead to new commercial products (e.g., through its Investor Catalyst Hub), the agency has an opportunity to vastly expand access by requiring that *commercial* entities agree to affordability and access provisions when licensing ARPA-H-funded intellectual property. Such expectations can be made clear before contracts are finalized. Importantly, this is feasible, as has been demonstrated by the French funder AFM-Téléthon who successfully negotiated affordable access to French patients to the gene therapy Zolgensma with Novartis.[1]

   ARPA-H could also support the establishment of multi-institutional working groups on improving access through the development of access plans, along with best practices for negotiation and implementation. In the US, access plans could include a "most-favored nation clause" that guarantees US patients do not pay more than those in peer countries. They could also enable greater support for specific populations (e.g., low-income Americans or Medicaid beneficiaries). To participate in these activities and ultimately enforce access provisions adequately, academic technology transfer offices will need additional resources and staff – another area ARPA-H investment can make a significant difference.

2. Supporting academic manufacturing capacity and collaboration. As CRISPR-based modalities expand, so will the need for manufacturing capabilities at academic centers to support early-phase clinical trials. Manufacturing in the academic setting can be significantly less expensive than at commercial sites, though still very expensive relative to research grants. All genetic therapies trace their origins back to academia[2], and many ultra-rare diseases are not commercially viable and may only be treatable in academic centers of excellence. ARPA-H has an opportunity to support manufacturing innovation and ensure that ultra-rare disease populations can access genetic therapies by investing in manufacturing capacity throughout the country and equipping facilities with new systems (e.g., closed, automated systems; systems that enable distributed manufacturing). ARPA-H could also fund a consortium of academic facilities that share data, streamline processes, and avoid duplicative efforts.

   Along the same lines, ARPA-H should support programs and public-private partnerships that unleash the platform potential of genetic therapies. While this certainly is a key scientific opportunity, proper implementation of a platform technology designation would

[1] License Agreement: By and between Généthon and AveXis, Inc. Accessed April 7, 2023. https://www.keionline.org/wp-content/uploads/avxs_Ex10_1-bank-info-redacted.pdf

[2] Vokinger KN, Avorn J, Kesselheim AS. Sources of Innovation in Gene Therapies - Approaches to Achieving Affordable Prices. N Engl J Med 2023; 388:292-295. doi: 10.1056/NEJMp2211729

dramatically increase access. ARPA-H is positioned to catalyze the riskier, but transformative, type of research needed to establish substantial evidence of safety of a platform.

3. Supporting the development of novel policy solutions. Genetic therapies constitute a new class of drugs that may be tailored to a small patient population (even a single patient) and have durable therapeutic effect after a single administration. As such, they differ considerably from small molecule drugs taken repeatedly over the disease course, and necessitate the development of updated regulatory frameworks, incentive structures, and reimbursement schemes. ARPA-H should support projects that investigate new policy proposals that tackle these issues.

It has been estimated that 40% of the 7,000+ rare diseases only affect 50 patients or less, making many commercially not viable. One policy innovation we envision is the creation of nimble regulatory tools for the timely and cost-appropriate administration of treatments in an academic/hospital setting. The European Hospital Exemption Rule provides an example of such a mechanism. Complementarily, CBER's OTP could have a dedicated office that oversees the development of N-of-Few treatments with no commercial viability in the academic setting. needed to further develop such policy solutions. There are also significant business challenges that may hold the field back. We are, therefore, particularly interested in exploring how incentive structures, such as the Orphan Drug Act, could be evolved to better support CGT development and competition that will reduce prices and increase patient access. Lastly, novel strategies for reimbursement are urgently needed to ensure access. Reimbursement schemes may have to be adapted to specific states, or policies that give federal CMS greater authority and leadership role in the reimbursement of genetic therapies may be needed. These and other policy options should be explored in further detail – ELSI research that ARPA-H funding could effectively catalyze.

4. Investing in novel business models. One key hurdle to affordable access to genetic therapies are the obligations of for-profit companies to maximize their shareholders' profits. Public benefit corporations, specifically, provide a transparent and sustainable strategy for the biotech sector to improve access to genetic therapies. This is not just hypothetical; several pharmaceutical companies have demonstrated that non-traditional business models can be successful. Civica Rx, which has implemented a healthcare utility model[3] to address generics shortages, Medicines360 and its domestic and global subsidiaries are another. The Mark Cuban Cost Plus Drug Company, a public benefit corporation, is making rapid headway in providing patients drugs at much lower costs, and has recently started working with health plans.[4,5] Caring Cross, a nonprofit entity developing place-of-care manufacturing solutions for genetic therapies globally, has recently also financed its first public benefit corporation that

[3] Dredge Carter, Scholtes Stefan. The Health Care Utility Model: A Novel Approach to Doing Business. NEJM Catal Innov Care Deliv. Published online July 8, 2021. Accessed March 3, 2023. https://catalyst.nejm.org/doi/full/10.1056/CAT.21.0189

[4] Constantino AK. Mark Cuban's pharmacy startup is actually making drugs less expensive. It's still working on solving the real problem. CNBC. Published July 28, 2022. Accessed February 17, 2023. https://www.cnbc.com/2022/07/28/mark-cuban-pharmacy-cost-plus-drugs-struggling-with-brand-name-drugs.html

[5] Gliadkovskaya A. Mark Cuban Cost Plus Drug Company announces first health plan partner, Capital Blue Cross. Fierce Pharma. Published October 6, 2022. https://www.fiercehealthcare.com/payers/mark-cuban-cost-plus-drug-company-bags-first-health-plan-partner

will serve as a contract development and manufacturing organization (CDMO) for GMP-compliant lentiviral vectors.

To enable this new way of doing business, a lower cost of capital is needed. The 90 / 10 Institute, a recently launched nonprofit think tank, is establishing new financial tools, models, and best practices to support and connect biomedical innovators and non-traditional capital sources that are aligned in their public benefit missions. The ecosystem of non-traditional business ventures is ripe for the kind of transformative government support that ARPA-H has the mandate to provide.

The government's investment in ARPA-H comes at an inflection point for biomedical research and biotechnology and the agency is optimally positioned to support innovations and creative solutions to the access challenges throughout the ecosystem. We applaud ARPA-H's leadership for committing to these issues and look forward to seeing the ELSI Initiative's goals infused throughout all programs.

On behalf of the Innovative Genomics Institute,

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