Innovative Genomics Institute

June 30, 2021

Notice Number:

NOT-TR-21-027

Request for Information (RFI): "Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies to Individuals with Rare Diseases"

National Center for Advancing Translational Sciences (NCATS)

Dear RFI Reviewers,

The Innovative Genomics Institute (IGI) is pleased to submit these comments in response to the issuance of a Request for Information (RFI): "Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies to Individuals with Rare Diseases" by the National Center for Advancing Translational Sciences (NCATS).

The IGI is a non-profit, academic research organization formed through a partnership between the University of California, Berkeley (UCB) and the University of California, San Francisco (UCSF), two of the world's leading scientific institutions. After co-developing CRISPR-based systems for rewriting DNA, Jennifer Doudna founded the IGI to bring together researchers in diverse disciplines with a powerful combined expertise to apply this technology to address some of humanity's greatest problems. In addition to our efforts in the life sciences, the IGI is committed to advancing and incorporating considerations of the ethical, legal, and social impacts of this transformational technology, and we place great emphasis on creating solutions that are equitable and accessible.

In addition to our expertise in basic research, the IGI also has translational and clinical work underway in the context of its mission to make CRISPR-Cas therapies the standard of medical care. Together with UCSF and UCLA, the IGI has a genome editing-based clinical trial for sickle cell disease (SCD) scheduled to dose the first subject this year—the sole such open investigational new drug (IND) held entirely by academic institutions in the hemoglobinopathies space. With an eye to addressing the gap between diagnosing rare disorders of the immune system and the impossibility of commercializing therapies for them, IGI scientists at UCSF have developed methods for editing primary human immune cells and are applying their advancements to therapies for ultra rare disease. The IGI Delivery Collective is developing new methods for directing genome editing effector molecules into target cells, hoping to remove one of the largest barriers to widespread application and implementation of genome editing – the therapeutic delivery step. To this end, the IGI is a hub for the Alliance for Therapies in Neuroscience to develop next-generation CRISPR-based therapeutics for neurodegeneration. Mindful that scalable deployment of any CRISPR-based approach will require appropriate genetic screening and monitoring, the IGI is also developing companion diagnostics to be deployed in our CLIA-licensed clinical laboratory.

We are thus excited by the NIH NCATS' interest in facilitating pathways for advanced therapies to positively impact the rare disease space and are particularly encouraged by the stated focus on equity and accessibility.

Some of us have had the opportunity to join the three-day webinar that accompanies this RFI, and have tried to add our thoughts in the context of what has been discussed so far when possible. We provide below some general recommendations and insights, along with specific responses to the questions posed by the RFI. As our expertise lies predominantly in CRISPR-based genome-editing approaches, we focus our response below on that space.

We welcome this opportunity and would be happy to further discuss any of our comments.

With best regards,

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Innovative Genomics Institute response to NCATS Request for Information (RFI): Facilitating the Early Diagnosis and Equitable Delivery of Gene-Targeted Therapies to Individuals with Rare Diseases

General Comments

Advances needed in genome-editing therapies and their regulation

Technology and Translation

The RFI and the webinar describe the challenge posed by the different pace of innovation between advances in gene-targeted therapies and advances in diagnostics. Gene-targeted therapies have advanced rapidly in the last 10 years, and the RFI contends that we are now at a point where methods like genome editing could theoretically be designed for any disease if the causal mutation is known. In contrast, our ability to diagnose more diseases with causal mutations is still trailing behind, and the national screening programs have not kept pace with this advancement in therapeutic design. While we agree that proper genetic diagnosis is intimately linked with the ability to design a new genome-editing therapy to target that disease, we caution that the current readiness of the gene-targeting field to respond to any individual with a newly diagnosed genetic disorder not be overstated. Specifically, the RFI states that "Clinicians, patients, and families may also not be aware that gene-targeted therapies are available for their specific rare disorder." In fact, gene-targeted therapies are not available for the vast majority of disorders. Even for those few genetic disorders that are currently targeted in clinical trials, not all people who have the disorder are eligible to participate. We routinely receive heartbreaking emails from families with a clear genetic diagnosis who are looking for gene-targeted treatment, and cannot help them.

We raise this point in order to emphasize that significant technological and regulatory innovations are still needed in order to reach a point, at least in the genome-editing field, where a genetic diagnosis *can* be followed by gene-targeted therapies. It is important to realistically calibrate expectations. Great strides have been made in *ex vivo* editing and hematologic and retinal systems, but additional innovations are needed to easily allow targeting of any tissue and to make any kind of modification, ideally without the need for specialized equipment or burdensome, expensive, and risky *ex vivo* procedures.

Regulatory Innovation

In addition to the technological advances needed, we will need to reimagine the regulatory approach. Currently, each new therapeutic must begin preclinical work, IND-enabling experiments, and chemistry, manufacturing and controls (CMC) relatively anew. This creates an expensive and time-intensive barrier to addressing new indications, especially those with a small target population from which to recoup these investments. The IGI has been an active participant in discussions around FDA regulation of genome-editing-based therapies, and has advocated an approach that takes advantage of the unique molecular mechanism that genome editing offers.

In 2018, we submitted a series of comments to the FDA (here and here) that describe a vision for a tiered-risk approach to regulation of genome-editing therapies that acknowledges the unique differences from viral transgene approaches of conventional gene therapy. We suggested that the FDA evaluate genetic therapies by assessing the components of each step of a therapy independently. Factors of each component may modify the overall risk profile of the end therapeutic. These factors include route of administration in the patient (whether administered systemically, localized, or *ex vivo*), persistence of editing reagents (whether the reagents are delivered as RNA, RNP, or DNA), and whether viral vectors are used for delivery. Mixing and matching choices for each of these components creates a spectrum of risk for which regulation ought to reflect that spectrum.

In addition, we've advocated that the modularity of genome editing reagents may be further leveraged by enabling sponsors to build on existing data or cross reference previous INDs when using the same manufacturing processes and many of the same procedures, cells, and components. For CRISPR-Cas genome editing, targeting a new gene for a new indication requires only a change in the sequence of the guide RNA—the Cas protein is constant and unchanged, as is the general structure and function of the guide. Thus, manufacturing procedures previously used to produce a clinically vetted guide RNA if used on a new sequence should not need to be re-evaluated nor should the toxicology of the reagents. However, because of the sequence-specific mechanism of CRISPR-Cas, changing the sequence of the guide RNA would significantly change the off-target profile. An additional burden of proof should be focused on thoroughly evaluating the off-target potential of a new guide. Regulating based on which elements of the therapy remain constant between different trials, and which are variable, will enable a sponsor to more easily develop therapies in a range of rare diseases that all target the same tissue system and use the same components with the exception of the guide sequence. Additional suggestions on innovating the regulatory system for rare disease can be found in part 3d of the section below where we address the specific questions asked by the RFI.

Dr. Peter Marks's vision for a "cookbook" and standard menu items that can be mixed and matched into new therapies is exactly the type of regulatory innovation that we have been hoping for. As has been noted by many others, this kind of development and curation of standard components by a federal agency would be particularly important if we ever want to reach a point where a genetic diagnosis is supplied, and then a genetic therapy is made.

This vision will also require more willingness to share data and collaborate between organizations, companies, and academia, so that a rising tide might lift all boats. The risk of not creating such a modular regulatory framework and willingness of industry to share data, particularly for rare diseases, comes at a major financial cost to developing new therapies, and a real human cost to those that continue to suffer without treatments.

Additional suggestions on a modular, plug-and-play regulatory framework for gene-targeted (particularly genome-editing) therapies for rare disease are as follows:

- Build shareable platforms of pre-approved components for tissue or organ systems, delivery mechanisms, effector molecules (e.g. Cas9 vs. Cas12), and procedures for drug administration. Those platforms could be owned and licensed by companies, or they could be built by a government facility/agency or non-profit. A more radical strategy could be to require that after a certain exclusivity period, all data used in the determination of safety and efficacy for a drug product in gene-targeted therapies be made public. That information could then become the basis of a registry of pre-approved components. Creative IP strategies may be needed to incentivize this level of data sharing.
- Identify target-agnostic variables, and then define what is needed for the target-specific variables. Existing INDs or data could be cross referenced within or between organizations for those target-agnostic variables, or developers could use off-the-shelf standard components and mix and match with target-specific elements. Those target-specific variables should be the main focus of evidence generation and burden of proof.
- In order to re-use or cross reference a component of a therapy, we must define how much prior experience with that component is needed in order for it to be considered as having a history of safe use. One way to do

this is to create tiered categories that require different levels of regulatory scrutiny depending on the amount of evidence available:

- Possible Tiers:
  - Highest scrutiny: A component that has never been used before
  - Medium scrutiny: A component that has been used once or a few times
  - No additional scrutiny to begin trials: A component that has a history of safe use based on being used N times (this threshold will need to be developed thoughtfully)
- Require that in exchange for access to any government developed standard components or a regulatory cookbook, developers must agree to submit and share data via a coordinated registry network so that as each new therapy enters clinical trials and each new person is dosed, the field can turn small datasets into much larger ones. Such a database would require centralization and management by a trusted third party, the NIH or FDA for example, or a professional society or trade association, such as ASGCT or ARM. The IGI is conducting a regulatory project with the American Society of Hematology (ASH) in collaboration with the FDA to explore the use of a coordinated registry network hosted by ASH for sickle cell disease in order to generate actionable, regulatory-grade, real-world evidence and to define what kinds of data points ought to be collected and submitted for genetic therapies in SCD. As we heard registries mentioned at the NCATS webinar, we would be happy to connect the organizers with the ASH Research Collaborative Data Hub and our joint project, as there may be opportunities for mutual learning.

Comments on the specified areas in the RFI:

1. ***To develop infrastructure for the efficient, effective, and equitable distribution of therapies it is important to define the following:***

   a. Consider who are the individuals that could benefit from gene-targeted therapies – now and in the future

   Current and near-term: monogenic disorders with a definitive mutation-disease link where the penetrance is high, and the burden of disease is severe.

   In the future: once safety and efficacy have significantly increased, and the risks are far outweighed by the benefits of undergoing genetic therapies, common diseases with known strong genetic components may become appropriate targets. Cell therapies that engineer the immune system may be extended to diseases beyond cancer, such as inflammatory bowel diseases, or rheumatoid arthritis. A growing list of diseases have known predisposition loci (e.g. ApoE4 and dementia) or strong modifier loci that are known to affect disease (e.g. PCSK9 and CAD, HSD17B13 and NASH). It will become important to properly assess the predictive strength of a mutation, the natural history of the disease, and the risk of inaction in order to avoid over-treating, or or falling prey to illusions of genetic determinism. These are also social and ethical questions and will require public and expert consultation.

   b. Consider what rare diseases or categories of rare diseases are most amenable to gene-targeted therapies – now and in the future

   The current categories of rare disease that are most amenable to gene-targeted therapies are those severe monogenic disorders with few or no safe and effective treatment options that affect organs where genetic therapies are currently feasible: inborn errors of immunity and other disorders of the blood, liver disease, disorders currently treated with ERT that can be treated using an IVPRP approach (hemophilia, the LSDs, PKU), some forms of neurodegeneration, pain, and retinopathies.

It will become feasible and appropriate to offer genetic therapies for the entire spectrum of severe disease once: delivery mechanisms improve and allow us to reach new cell and organ systems, those platforms are made available under a modular regulatory system, our understanding of the genetic basis of different diseases advances, and the predictability of penetrance increases.

c. Consider when is the optimal time to identify individuals who could benefit from gene-targeted therapies (e.g., newborn screening)

In general, the earlier a disease is treated, the better. Sickle cell disease presents a useful example. In our interactions with people living with SCD and their physicians, it is clear that even after a successful bone marrow transplant or gene therapy, many adults still experience severe joint pain and symptoms associated with permanent organ and tissue damage that are not reversible by fixing cell sickling. For this disease and many others, the earlier a curative treatment can be administered, the more likely permanent damage can be prevented.

Delays in diagnosis can thus mean the cumulation of irreversible damage. However, for many diseases this presents a dilemma. Not all mutations that are highly *correlated* with disease definitively *determine* that an individual will develop that disease state. The goal is to diagnose and treat as early as possible, but this must be balanced against predictive outcomes that put patients at risk without the certainty of disease burden.

2. Consider what type of infrastructure is required to disseminate gene-targeted therapies to individuals with rare diseases in need of treatment using the following:

a. Consider the current mechanisms for diagnosing and identifying individuals with rare diseases for gene-targeted therapies

The inefficiency of current mechanisms for diagnosing individuals with rare diseases is a major challenge in clinical medicine. Given the ultra-low prevalence of rare genetic diseases, the initial symptoms of a particular disorder can be mistaken for more common diseases, particularly since many symptoms may be shared. As a consequence, there are often long delays in arriving at the correct diagnosis. Aside from lack of physician expertise, delays in diagnosis result from delays in patients/families seeking care (due to cost, education, and overall awareness), delays in referring patients to centers of excellence, geographic isolation (not being near centers of excellence), and limited access to genetic/genomic services.

b. Consider how can the early diagnostic process be improved; Consider other models that can be developed and used to better identify individuals who can benefit from rare disease therapies in a timely manner; Consider what other methods/platforms to identify such individuals that could be leveraged and list and/or describe.

California has a strong newborn screening program (NBS) as do other states. Building on this program, and carefully considering what warrants mandating versus making voluntary will be important. The advent of cost-efficient sequencing suggests the notion of expanding NBS to whole exome sequencing (WES) or whole genome sequencing (WGS). The concept of a mandatory newborn WGS program coupled with data storage in a national database was discussed on the last day of the webinar. The discussant noted that mandatory may be the only way to achieve equality in diagnosis. However, this trades one set of ethical concerns for another. Because there is no specific diagnosis that a nation-wide mandatory WGS program would be testing for, it could be considered closer to research, as it would create a large dataset of individual genomes coupled with their health records that could facilitate identification of new disease alleles to be diagnosed in the future. Mandating participation in such a program would be akin to mandating participation in research—something forbidden by the founding principles of the Belmont report and the protections for human subjects in research. We encourage the workgroups to consider alternative mechanisms.

IGI's work on the ethics and social considerations of genome editing has exposed us to a wide range of perspectives that include historically-grounded and legitimate concerns around commercial and government use of whole genome sequencing. Privacy and ownership of one's own genetic information is incredibly important to a wide range of people. A national database of the genomes and related PHI of all of a nation's

citizens could pose a security risk beyond that of any health data breach so far. Fears of genetic discrimination are grounded in the realities of history. Atrocities of the American eugenics movement continued until the 1980s, when the last state-forced sterilization of an "unfit" individual occurred. Until very recent history, insurance companies were allowed to deny coverage to individuals with pre-existing conditions. The Genetic Information Nondiscrimination Act was put in place to address some of these concerns, but there are well-known gaps in its scope, and its permanence as a protective instrument should not be taken for granted as members of congress have tried to reverse its protections. Personal genomes also have a complicated history for indigenous communities, where their ancestry has been simultaneously used to prevent their access to government programs, and then later required as proof to determine who can be called "indigenous" and therefore benefit from certain government programs. Perhaps ironically, many of the same groups of people that one might try to reach by making a newborn WGS program mandatory are the same people that have reasons to be concerned with a government-run mandated genomic surveillance program.

A possible middle ground might be to build, adequately fund, and ensure insurance coverage for a *voluntary* national WGS program, potentially using a hub and spoke model for centers of excellence. In addition to voluntary newborn sequencing, such a program might be particularly useful for those individuals who have a symptomatic undiagnosed disease, and could be set up to connect participants with a bespoke genetic therapy consortium (as Dr. Peter Marks envisions) so that there is a clear link between participation and potential benefit.

In preparing our response to this RFI, we discussed how clinicians are often faced with a decision about what kind of diagnostic panels to order for a symptomatic patient, and whether whole exome sequencing should just be the standard for undiagnosed disease. There are endless examples of clinicians ordering test after test, but as soon as they finally do whole exome sequencing, they find a variant of interest. However, support for interpretation of the data is variable from hospital to hospital. Such a national program could help overcome the interpretation expertise gaps, and would shorten the diagnostic odyssey. In the best case, it could immediately connect a diagnosis with a company/organization to make a gene-targeted treatment.

At the same time, additional research into the genetic basis of disease is absolutely critical to expand the list of known pathogenic alleles. A challenge for WGS/WES in clinical settings is how to interpret variants of uncertain significance (VUS). While some patients suffer from undiagnosed disease that doesn't match a known phenotype, others may exhibit a phenotype from a known rare disease, but when genetic tests are run, it is found that rather than the known variant, the patient contains new variants that are not well documented or understood. Currently, there is no unified system to (1) sequence and (2) experimentally validate the VUS as causative. A national voluntary WGS program, building on the Undiagnosed Diseases Network, could do this work. Such research could feed into an expanded screening program that *offers* newborn screening for known genetic disease, but for a wider list than is currently mandated in the RUSP.

Gene panels for an expanded newborn screening program (disorders beyond those listed in the RUSP) could be designed to assay for those known alleles that meet certain criteria. These criteria ought to incorporate the five-tiered variant interpretation standards that classify variants as benign all the way to pathogenic (ClinVar, dbSNP), and should take into account information on natural history, penetrance, and severity of the diseases to avoid over-diagnosis and financial and emotional harm to patients and families. Initial efforts should focus on those alleles that have clear significance and high penetrance for disorders that are severe and medically actionable. Additionally, investments should be made to spur innovation to make simpler diagnostic tests that can be better scaled, for lower prices, in order to ensure that all health centers, even those in the least resourced settings, are able to offer such a screening program.

c. Consider if there are currently any public/private partnerships in existence that support gene-targeted therapies and list and/or describe.

Two recent public-private partnerships at UC Berkeley and UCSF may be relevant. First, UCSF and UC Berkeley have created a research partnership with Genentech and Roche Holding AG, to advance new therapies for brain diseases and disorders of the central nervous system (CNS), such as Alzheimer's, Parkinson's, Huntington's, ALS and autism. This 10-year collaboration is housed in the Weill Neurohub and named the Alliance for Therapies in Neuroscience (ATN).

Second, members of IGI have also facilitated a unique public-private partnership with GlaxoSmithKline (GSK) to create a new Laboratory for Genomics Research (LGR) at UCSF. The LGR is a five-year collaboration with UC Berkeley and UCSF to establish a laboratory where industry and academic scientists can collaborate to study the genome-disease interface using CRISPR in order to accelerate the discovery of new medicines.

d. Consider if a system that provides for a few patients can transition to a system that is comprehensive without becoming insolvent

We believe it is possible if the system explicitly focuses on innovation that drives towards expanded access, affordability, and scalability.

e. Consider the current means of communicating information related to gene-targeted therapies to primary care physicians and other healthcare providers

We have found that awareness of current genome-editing clinical trials and general approaches for genome-editing therapies is surprisingly low among primary care physicians and pathologists. Even for an area that has the most genome-editing clinical trials—blood disorders—we found that many blood bank and transfusion professionals were unaware of CRISPR and genome editing. To reach this audience, we published a review in a journal read by that target demographic. Additional methods ought to be funded and employed, perhaps through a consortium model with open access materials, as Vence Bonham has proposed.

f. Consider methods we should use to communicate with healthcare providers, patients, and families regarding gene-targeted therapies and list and/or describe

As the webinar highlighted, families with members suffering from an undiagnosed or rare disease face an uphill battle to diagnosis and an even steeper battle to navigate what treatments are available and what technologies might be used to create novel therapies where there aren't any available. As an institute founded by Nobel Prize winner and co-developer of CRISPR-based genome editing Jennifer Doudna, we have received hundreds of emails from parents with desperately ill children desperately eager for help. We have tried to respond thoughtfully to each and every email, provide realistic evaluation of whether genome editing can be of use now or in the future, and point parents toward whatever resources we know of. We've compiled what we've learned about existing resources during this process into a page on our website for patients and families. But a better mechanism is needed.

The field needs a centralized program that is easy to find, and that can take on this enormous challenge to guide parents and physicians through the journey from diagnosis to identifying options for treatment. The NIH would be best positioned to be a neutral, trusted source of information that could connect clinicaltrials.gov or a database of disease alleles and VUSs with scientist-clinicians that have domain-specific knowledge and the time, funding, and ability to build a new therapy in the vein of Tim Yu's work for Mila. Such an education, information, and data hub would need to be well staffed and could be connected with a non-profit or public-private partnership in the vein of the "Bespoke Gene Therapies Consortium" proposed by Dr. Marks. Without a centralized, well funded, and innovatively regulated (see our comments on plug-and-play modules) location to create individualized therapies, it will be nearly impossible for most families to create a successful partnership like the one between Mila's family and Tim Yu.

Such a resource could build on and integrate the NIH's Undiagnosed Diseases Network (UDN), the NCATS' Rare Diseases Clinical Research Network (RDCRN), and advocacy organizations that have done a lot of work to compile resources and information for families such as the Genetic Alliance.

3. Consider the methods that will ensure equitable access to gene-targeted therapies

a. Consider how can we address potential disparities in access to these therapies

The current system of drug development in the US relies on incentives to innovate that are based on the potential to profit. This system is fundamentally at odds with developing drugs for small target populations. In order to stand a chance of recouping investment costs and making a modest profit, companies have to charge exorbitant prices that the fractured US insurance system is not built to cover. If rare diseases are not attractive candidates for companies, academic programs may be better suited to develop gene-targeted therapies for rare disease. However, even in cases where academic programs have developed new treatments for rare disease, they need clinical trial sponsors and post-approval partners to administer those treatments, and in some cases, those sponsors have shelved a promising therapy that could save patients because it could not make money. This is a failure and a barrier to wide access.

Is there a role for the government or non-profits in developing (and administering) therapies for disease spaces that are not financially profitable? Two examples may be of use to the committee. The first is a new non-profit and model proposed by Stan Crooke for antisense oligonucleotide therapies for ultra rare disease.

The second example is the California Institute for Regenerative Medicine (CIRM). CIRM is a state program, funded by the California tax payers, that has sponsored numerous genome-editing (and gene therapy) pre-clinical as well as clinical trial work. In fact, CIRM funds our current UCSF-UCLA-IGI SCD clinical trial. With a renewed funding stream, CIRM is considering whether and how to make a California-funded platform technology center that can manufacture and administer gene-targeted therapies for rare diseases. This might look like capability hubs that leverage non-profit institutions and novel forms of public-private partnerships to deliver cures.

Alternatively, the committee may want to consider whether creating a plug-and-play regulatory system could be enough to incentivize companies to invest in creating genome-editing therapies for ultra rare diseases. Perhaps such a system would enable a company to focus on creating a platform that could address many different diseases of a similar organ system by simply changing a guide RNA or a variable component. Doing so might make the cost of developing “N of 1” therapies leverageable to many different rare diseases.

b. Consider what can be done to encourage collaboration and increased communication among various stakeholders.

Mechanisms that incentivize sharing and collaboration in exchange for funding or access to certain resources, data, or other advantages have been effective, as have those that bring like-minded individuals together around a common goal. CIRM has created the Alpha Stem Cell Clinics Network that brings together investigators and clinics funded by CIRM to share best practices and create a community of practice. DARPA has similarly funded mechanisms for teaming up to deliver cures.

c. Consider what currently facilitates provision of, or inversely limits access to targeted therapies for patients with rare diseases and list and/or describe

Throughout this response, we discuss the limits placed on scalability and cost for genome-editing products, and therefore access, stemming from the current regulatory system. Each step of developing and testing a new genome-editing therapy is extremely costly and still done within the same regulatory framework that has existed for viral gene therapy since the 1990s. A fundamental shift in how therapies for ultra rare diseases are regulated is needed.

Other social contexts create further limitations to access to targeted therapies for patients with rare disease. Many of the new gene-targeted therapies for ultra rare disease have been created through a similar pathway: a parent of a child with an undiagnosed or untreatable rare disease undertakes the enormous task of researching the disorder, finding specialists and domain experts, and then

crowdsourcing or founding a non-profit to fund research to create individualized therapies for their child and others like them. Without these highly motivated families and their tireless efforts to create teams and find funding, therapies like Milasen or biotech companies like Phoenix Nest, founded by a mom of a child with Sanfilippo syndrome, would not be possible. But this pathway is inherently biased to families of privilege. White, affluent parents are more likely to be able to invest the time and money into such a journey, and are more likely to have connections with people in biotech or pharma to help them create new therapies. Thus, the journey itself is exclusionary to those in disadvantaged communities. Creating a centralized non-profit or government collaborative to facilitate patient and family information, education, diagnosis, and treatment at no cost would also go a long way in making bespoke therapies more equitable.

d. Consider what type of innovations are needed to enable and support development of gene-targeted therapies in a timely fashion. In general, consider what needs to be improved to deliver gene-targeted therapies to individuals who need them in an efficient, effective, equitable, and timely manner

Below, we further elaborate on our comments regarding innovation needed to the regulatory system and to the technology of genome-editing therapies. These suggestions are focused on solutions to the problem of academic innovation lacking a clear mechanism for translation to the clinic, manufacturing, and administration post-approval. Whatever large-scale initiatives exist to fund innovation must think forward to who will use them and how they will get there. Standardization for assays needed to move to IND, or plug-and-play CMC, would widen the door to non-traditional ways of moving an academic proof-of-concept project to the clinic. Such standards need to be vetted by the FDA, but nimble enough to respond to advances in assay development.

Innovations needed:

- Products need to transition from gene therapy to genome editing, from viral delivery to nonviral delivery, and from *ex vivo* to *in vivo*.
- **Novel molecular delivery and therapeutic administration methods**. For example, we need to develop *ex vivo*, closed-loop systems that cut down on the equipment, GMP, and resources needed to edit autologous cells and which could be more easily deployed in lower resourced hospitals, not just large academic medical centers. We also need to create nonviral vectors that deliver therapies systemically *in vivo* beyond the liver in order to begin developing cures for disorders in more tissue and organ systems. Because of the way viral vectors are manufactured and the CMC involved, neither adeno-associated virus nor lentivirus will ever be scalable at the level needed to treat the number of individuals with genetically tractable disease. As a field, there needs to be greater emphasis on advancing non-viral genome editing.
- **Expand the genome-editing toolbox to create more modular components that can go from allele to desired clinic-grade outcome**. For those components to be truly plug-and-play, we need regulatory changes that may look like the following:
  - *CMC for critical reagents*
    - In our comments to the FDA, we elaborate on what types of changes in CMC and GMP requirements are needed for critical reagents. For example, for a soluble protein such as Cas9, which is invariable between indications, regulation should match what is done in the antibody manufacturing space where manufacturing is completely stereotypical and ORF-agnostic. Rather than starting GMP at the plasmid level, GMP is started at the clone level. The same shift for genome-editing reagents could have a significant cost and time savings. Further assessment is needed to determine which critical quality attributes (CQAs) truly matter for safety in which contexts, and then adjust CMC requirements accordingly.
    - We need uniform standards for the CQAs of critical reagents. For example, currently there is no standard CMC-compliant way to measure the sequence of the gRNA.

        - *An FDA-curated, standardized menu of preclinical assays*. These include IND-enabling toxicology studies, particularly for editing T cells *ex vivo*, editing hematopoietic stem and progenitor cells *ex vivo*, editing the liver *in vivo*, and editing retinal cells *in vivo*. We also need to create improved organoid systems to get away from costly primate experiments for *ex vivo* efficacy and safety.
        - *Standardization and agreement on how to assess individual-variation-imposed risk of unique off-target events and uniform standards for long-term follow-up at the genomic level*. Both of these issues are being discussed in our collaboration with ASH on "Accelerating Innovations For Sickle Cell Disease Using Real World Evidence."
    - Additionally, the high bar for GMP for critical reagents means that a few companies corner the market with extremely high price tags for CRISPR effectors and guide RNAs. NCATS should explore whether investments in not-for-profit CROs or federally funded manufacturing are needed to provide the critical reagents for minimal cost for development of therapies for indications that are not profitable and therefore will not be tackled by industry.

4. In general, consider what needs to be improved to deliver gene-targeted therapies to individuals who need them in an efficient, effective, equitable, and timely manner

See "General Comments" at the beginning of this submission.

Additionally, it is important to be conscious of the context of the American healthcare system, and how it interacts with the envisioned goals of this initiative. There are healthcare system challenges that aren't specific to gene-targeted therapies or diagnostics for them, and are probably one of the largest hurdles in equitable access. Who has health insurance, who comes in to the doctor at all, who wants screening? This reality poses constraints that NCATS will have to work within.

Another challenge we did not notice discussed in the webinar is how informed consent practices are impacted or ought to be modified for ultra rare diseases. Many of the examples of individualized therapies have been achieved through a similar story: a family with a member that has an undiagnosed disease crowd-sources funding and finds a scientist-clinician to work closely with to develop a therapy for their family member. In these situations, the relationship between clinical trial participant, and the clinician is significantly different from other, larger trials, where the therapy was developed as part of a broader program. Studies into the psychology and ethics of patient-clinician relationships and the compression from bench to bedside, suggest that such a unique situation may present unique challenges to truly informed consent. Families may experience unconscious undue pressure by their personal investment in the project and the clinician, and their ability to evaluate risks and benefits may be compromised. More work ought to go into studying how the informed consent process might be adapted for this kind of ultra rare disease situation.