ELSI Friday Forum Summary: Fair Access and Equity of Individualized Interventions for Ultrarare Genetic Conditions

Event Overview

The ELSI Friday Forum, organized by the Center for ELSI Resources and Analysis (CERA), was held in September 2023. This monthly forum, funded by the National Human Genome Research Institute at NIH and managed by teams at Stanford, Columbia University, and the Hastings Center, focuses on ethical, legal, and social implications of genetics and genomics research. This session addressed "Fair Access and Equity of Individualized Interventions for Ultrarare Genetic Conditions" through presentations and a moderated discussion format. The forum featured expert speakers Ingrid Holm, MD, MPH, Professor of Pediatrics at Harvard Medical School and Associate in Pediatrics in the Division of Genetics and Genomics and Division of Endocrinology at Boston Children's Hospital, and Alison Bateman-House, PhD, MPH, MA, Assistant Professor in the Division of Medical Ethics at NYU Grossman School of Medicine. The session was moderated by Meghan Halley, PhD, MPH, a Senior Research Scholar at the Center for Biomedical Ethics at Stanford University, with introductory remarks by Sandra Soo-Jin Lee, PhD, co-director of CERA.

The forum aimed to explore ethical challenges surrounding the development of individualized therapeutics for ultrarare genetic conditions, particularly regarding safety, equity, and access. Dr. Halley framed the discussion by highlighting that rare diseases collectively affect 25-30 million Americans, with approximately 80% having known or suspected genetic origins. Though rare diseases are responsible for a third of deaths in children before the age of one, over 90% lack FDA-approved therapies. The session specifically focused on "ultrarare" conditions (affecting 1-20 patients per million people) and the emerging field of individualized treatments for these conditions.

Context: The Development of Individualized Therapeutics

Dr. Halley introduced the groundbreaking case of Mila Makovec, an 8-year-old girl with Batten Disease who received the first individualized antisense oligonucleotide (ASO) therapy developed specifically for her genetic variant in 2018. This therapy, named "Milasen," was developed in just one year at an estimated cost of $3 million funded by a charitable organization. While Mila showed improvement, she was not cured and passed away in 2021. This case represents both the promise and challenges of personalized treatments for ultrarare conditions.

Key Insights from Dr. Ingrid Holm

Dr. Holm explained the scientific foundation of ASO therapies, which are synthetic DNA or RNA sequences that can be customized to target specific genetic variants. She emphasized several important points about these therapies:

- ASO therapies are "programmable" treatments that can be tailored to individual genetic variants
- Most candidates are for neurological disorders that cause developmental delay and eventually death
- Symptoms manifest in infancy and are progressive; early treatment can lessen or prevent symptoms
- Not all genetic variants are amenable to ASO therapy—they are highly variant-specific
- These treatments represent true N-of-1 (individualized) therapies

Dr. Holm identified several ethical challenges in this emerging field:

1. **Evidence and efficacy questions**: What evidence is needed before implementing these treatments? How should efficacy be evaluated when only one person receives the treatment?
2. **Clinical trial vs. clinical care boundary**: Is treating a single patient a clinical trial or simply clinical care? Dr. Holm suggested that "providing the best possible care to an individual patient could inherently be integrated with gaining knowledge… so maybe there isn't as much of a boundary."
3. **Patient perspectives**: Issues of therapeutic optimism, informed consent, and communication of risks and uncertainties are particularly challenging.
4. **Decision-making challenges**: Questions around when to treat in disease progression, whether urgency should factor into decisions, and whether potential benefit to future patients should be considered.
5. **Societal concerns**: Justice and fairness in allocation strategies, equity and inclusion, funding questions, and potential exacerbation of health disparities without access to N-of-1 therapies.
6. **Pediatric considerations**: How to weigh harms against benefits for children who cannot assent, determining the appropriate degree of child engagement in decision-making, and considerations for their future autonomy.

Dr. Holm described her current grant work with Dr. Timothy Yu, the developer of Milasen, to provide ethical guidance for the development of some of these therapies through a stakeholder-based approach that aims to "catalog and examine the range of ELSI arising in the development of individualized rare therapies from the perspective of diverse stakeholders" and subsequently develop ELSI guidance for N-of-1 therapies.

Key Insights from Dr. Alison Bateman-House

Dr. Bateman-House described her role as a volunteer ethicist for the n-Lorem Foundation, a charitable foundation that develops ASO therapies and provides them for free to qualifying patients. She highlighted two major ethical challenges beyond cost:

1. **Access to diagnosis**: Before patients can even be considered for individualized therapies, they need access to genetic testing, genetic counseling, specialists, and proper diagnosis—all areas with significant inequities. It can take years to get a diagnosis, which is necessary for a child before "getting into the pipeline for one of these N-of-few interventions."
2. **Regulatory framework questions**: When should therapeutics follow traditional drug development pathways versus individualized approaches? Dr. Bateman-House asked, "Where do we draw the line between a rare disease that does go through that normal process to bring a drug to market and an ultra-rare disease or an ultra-ultra-rare disease in which we forego that process?"

Dr. Bateman-House noted that there is no financial incentive for companies to bring N-of-few therapeutics to market due to small population sizes. She highlighted FDA's acknowledgment that "individualized ASO drug products are not expected to follow the traditional investigational phases of drug development," while raising important questions about safety standards, dose selection, and efficacy evaluation in these cases. Even in rapidly progressing, fatal illnesses, there must be some assurance of safety with respect to severe complications or death. Dr. Bateman-House posed the question, "where do we draw the line?"

She also described evolving and conflicting standards regarding what conditions qualify for individualized approaches versus clinical trials:

- FDA guidance for ASO drug products focuses on "one or two patients"
- n-Lorem uses a cutoff of N-of-30 (what they term "nano-rare")
- There is growing tension about where to draw these lines

She emphasized the challenges of justifying different regulatory approaches based on disease prevalence, making a provocative point: "Is it fair to say because we think we can make money off of selling a product to your group, we need you to go this way versus we don't think we're going to be able to make money off of your group so we will allow you to go through the other way?"

Highlights from the Q&A Session

Defining stakeholders in ethical discussions When asked about her approach to deciding who should be at the table in these kinds of discussions, Dr. Holm explained that her research includes diverse groups impacted by or involved in different aspects of N-of-1 therapies:

- Academic institutions and site teams conducting ASO treatments
- Parents of children with rare diseases
- Ethics experts
- Oversight experts (e.g., institutional review boards)
- Representatives from foundations and advocacy groups

Financial models for increasing access Dr. Bateman-House described n-Lorem's nonprofit model where a foundation develops ASOs and provides them for free to qualifying patients,

while noting its limitations. She explained that n-Lorem has a mutually beneficial relationship with Ionis Pharmaceuticals, a commercial ASO developer, creating a pathway where cases with higher prevalence than 30 might be referred to Ionis for commercial development. This relationship has been a source of confusion for parents, and Dr. Bateman-House emphasized the need for transparency about data access and usage. She also noted that some argue commercial payers should fund these therapies as cost-saving measures in the long run, similar to gene therapies, but skepticism remains about proving their effectiveness upfront.

Balancing progress with equity When asked about tension between advancing the science and ensuring equity, both speakers offered nuanced perspectives:

Dr. Holm emphasized that equity considerations should not be postponed: "We want to give everybody an opportunity to be involved in developing these treatments... It's really not about trying it on the rich people first."

Dr. Bateman-House acknowledged real-world constraints: "I don't think we should halt progress in this field while we try to attain some nirvana… I'm okay with some select few being the first as this field develops as long as there is both ongoing discussion [that] we are only addressing like a very small tip of the iceberg, and we need to figure out how to reach the rest of the iceberg as soon as possible."

Both agreed that early cases like Mila's create awareness that helps expand access to others.

Individualized therapies versus "Right to Try" Dr. Bateman-House differentiated between the ideology of "right to try" and the specific Right to Try law. While the ideology of patients seeking innovative treatments aligns with individualized therapies, where patients with no other options seek to try novel approaches despite significant uncertainty, she argued that the Right to Try law is inappropriate for these cases because:

- The doctor serves as both sponsor and physician, creating conflicts of interest
- These situations lack adequate oversight
- The expanded access pathway (which all individualized therapies have used to date) provides more appropriate FDA and IRB oversight for these novel treatments

Overall Themes and Takeaways

Several recurring themes emerged throughout the discussion:

1. **Tension between innovation and equity**: Both speakers acknowledged the challenge of advancing potentially life-saving treatments while ensuring broad and fair access.
2. **Unique regulatory challenges**: Individualized therapies don't fit neatly into existing regulatory frameworks, requiring new approaches to ensure safety while enabling access.
3. **Multiple barriers to access**: Beyond cost, significant barriers include access to diagnosis, genetic testing, counseling, and specialty care.

4. **Expanding definitions**: As technology advances, the definitions of "ultra-rare" conditions and acceptable approaches continue to evolve, raising questions about where lines should be drawn.
5. **Need for stakeholder engagement**: Both speakers emphasized the importance of including diverse perspectives in developing ethical frameworks for these novel therapies.

The discussion revealed both promise and caution regarding individualized treatments for ultrarare genetic conditions. While these therapies offer hope for previously untreatable conditions, significant challenges remain in ensuring their safe, ethical, and equitable development and delivery. The forum highlighted the need for ongoing dialogue among diverse stakeholders to address these complex issues as the field continues to evolve.