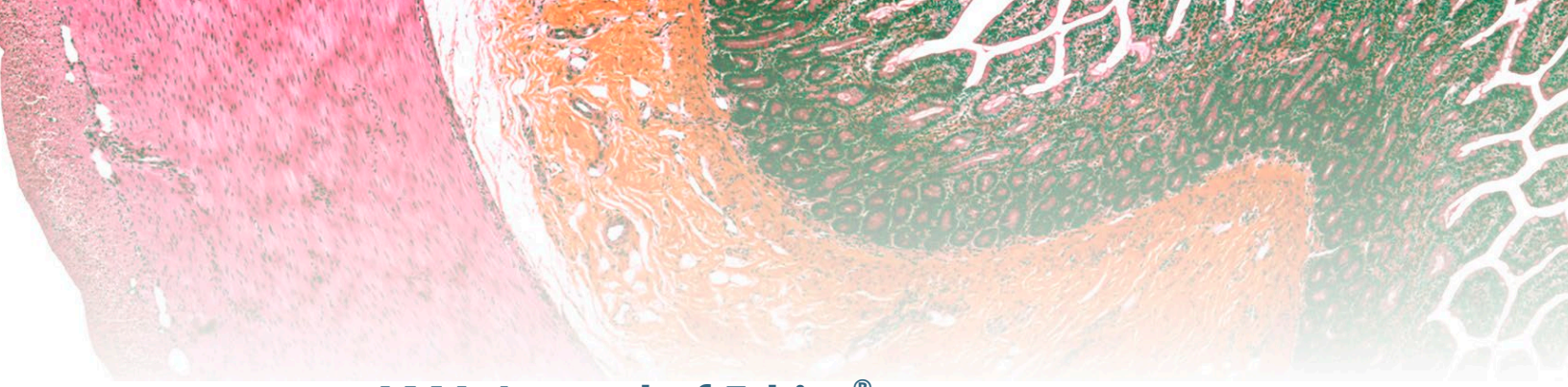

AMA Journal of Ethics®
December 2025, Volume 27, Number 12: E881-883

LETTER TO THE EDITOR

Response to "Response to 'Is the UDN N-of-1 Enterprise Ethically Justifiable?'"

Gianna Gordon and Lisa Kearns, MS, MA

Based on our review of the correspondence from the Undiagnosed Diseases Network (UDN) regarding our article, "Is the UDN N-of-1 Enterprise Ethically Justifiable?" we give a point-by-point response to their summaries of our arguments (in italics) below.

1. *With a centralized institutional review board (IRB), there is no case-by-case review of participants*. We appreciate the strict system-level oversight of consent processes that sites employ yet worry about the application of those processes at the participant level. Extremely heterogeneous patient populations ethically require close oversight by clinicians and researchers with appropriate expertise.

2. *Participants may not understand N-of-1 research or outcomes; parents may feel internal pressure to continue participation*. Our concern is whether ethical best practices are sufficient for the UDN's participants. They are in an especially vulnerable position, as is anyone with a rare disease. It is an ethics issue if patients feel pressure to stay in a study because they have built up, in their own minds, the potential benefits of the study.

3. *Participants' symptoms are difficult to anonymize, and data sharing can threaten insurance coverage*. Because UDN patients have such rare conditions and data may be requested from family members, guaranteed anonymity of data is not possible, even with safeguards in place. (This is true of other databanks.) It is not our intention to distress families, but withholding potential consequences of a data breach violates ethical principles of autonomy and beneficence. Our mentioning the effects of a potential privacy violation isn't distressing, but the fact that it could happen is.

4. *Minority and rural participants are not well-represented in the program; cost is a barrier to participation*. We agree that underrepresentation is an ongoing ethical concern in all drug development in the United States. Even with assistance, UDN participants could still be on the hook for patient services costs steep enough to prevent their participation.

5. *Need for network external advisors.* We're not clear about what the authors are referring to here. To bolster patient protections, especially for informed consent, we suggested that the UDN create a dedicated oversight committee comprising members with relevant expertise. They would provide guidance to UDN researchers, physicians, and patients, not to the National Institutes of Health.

6. *The UDN benefits few participants.* We agree, and we applauded both the UDN's creation of foundational knowledge and its freely sharing it. We also mention the benefits to undiagnosed patients of having certain conditions ruled out.

7. *UDN federal funding is not justifiable due to the small and select group of individuals helped.* We did not say or imply that patients with undiagnosed diseases are any less deserving than anyone else. Rather, we question the ethics of *publicly* funding the UDN, given the limited resources available for health care in this country. We also would never disregard the contributions of rare disease research. UDN patients are not less deserving of public funding but rather, according to the ethical principle of justice, conditions affecting larger groups of the population—some comprising hundreds of thousands of people—may warrant a larger share of limited resources. We add that we find the United States' choice to limit resources for health care to be ethically indefensible.

We thank the authors for their careful reading of our article and for their comments. We admire the UDN's efforts and the impressive success it has achieved. As we acknowledged, the low percentage of patients helped are actual patients and families, whose arduous search for a diagnosis was ended by the UDN's researchers.

Gianna Gordon is a first-year student at the University of Chicago in Illinois, where she is studying biological sciences and genetics. She is a 2025 graduate of Léman Manhattan Preparatory School in New York City, an independent K-12 international baccalaureate world school, where she participated in the Science Research Program. Her research interests include bioethics and genetic therapy for ultra-rare diseases.

Lisa Kearns, MS, MA is the senior research associate in the Division of Medical Ethics at NYU Grossman School of Medicine in New York City and the associate director of the division's High School Bioethics Project. She is also a member of the division's working groups on Compassionate Use and Preapproval Access and on Pediatric Gene Therapy and Medical Ethics. For the past 10 years, she has studied ethical issues in preapproval access to investigational drugs, including gene therapies and individualized genetic interventions.

Citation
AMA J Ethics. 2025;27(12):E881-883.

DOI
10.1001/amajethics.2025.881.

Acknowledgements

Conflict of Interest Disclosure
Contributors disclosed no conflicts of interest relevant to the content.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

ISSN 2376-6980