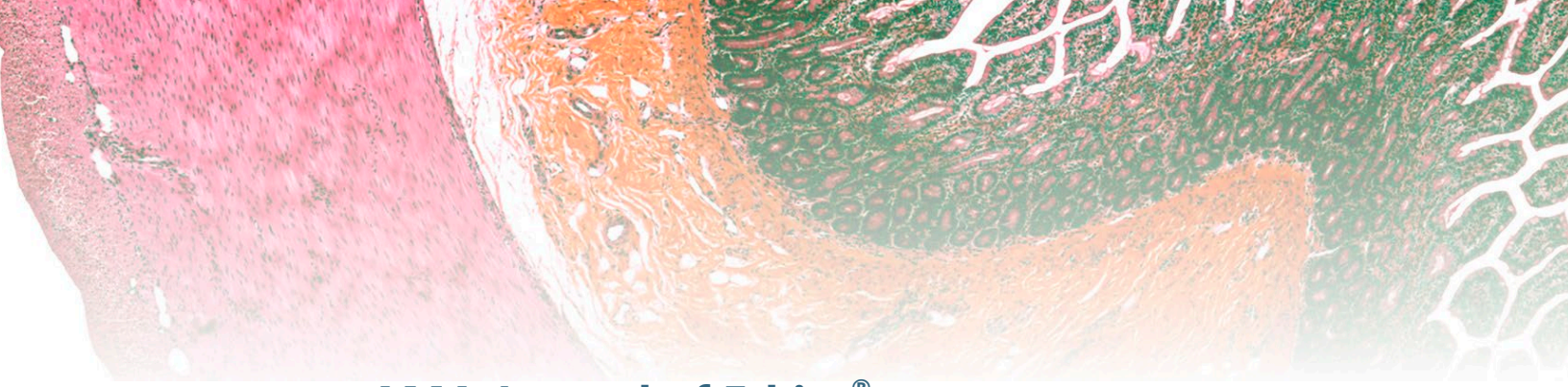

AMA Journal of Ethics®
December 2025, Volume 27, Number 12: E876-878

LETTER TO THE EDITOR

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

Undiagnosed Diseases Network

We write to respond to several inaccuracies and claims (summarized in italics) in the Gordon and Kearns article[1] regarding processes, risks, and benefits of the Undiagnosed Diseases Network (UDN).

1. *With a centralized institutional review board (IRB), there is no case-by-case review of participants*. Case-by-case reviews, including of adherence to eligibility criteria, consent practices, and design and execution of clinical evaluations, are performed at each UDN site by principal investigators who report to institutional and central institutional review boards (IRBs).

2. *Participants may not understand N-of-1 research or outcomes; parents may feel internal pressure to continue participation*. The UDN consent processes adhere to established ethics best-practices,[2] including facilitating understanding of both the research and the possibility of not obtaining a diagnosis or treatment.

3. *Participants' symptoms are difficult to anonymize, and data sharing can threaten insurance coverage*. External sharing of UDN phenotypic data in data repositories involves deidentified data and standardized Human Phenotype Ontology terms and is compliant with IRB and legal requirements. Claiming that insurance coverage might be affected by data sharing adds an unsubstantiated barrier to already-distressed families' participation.

4. *Minority and rural participants are not well-represented in the program; cost is a barrier to participation*. Lack of minority representation affects many clinical trials. The UDN has recently established community partnerships to enroll participants with health disparities and has always prioritized NIH funds to cover patient costs for under- and uninsured participants.[3]

5. *Need for network external advisors.* Although UDN primary investigators are experts in rare and ultra-rare diseases, since its initiation the network has also had an external scientific advisory panel comprising non-UDN experts in rare and ultra-rare diseases and genomics to provide guidance to the NIH.[4]

6. *The UDN benefits few participants.* Rare and ultra-rare diseases affect approximately 30 million people in the United States,[5,6] many of whom remain undiagnosed. Although the UDN cannot evaluate all individuals, its methods and

successes provide scientific and clinical models for both diagnosed and undiagnosed rare disease research.[7,8,9,10,11]

7. *UDN federal funding is not justifiable due to the small and selected group of individuals helped.* This argument overlooks its initiatives to increase equity.[3] It also employs zero-sum thinking by casting individuals with undiagnosed diseases as less deserving of federal funding, and it disregards the contribution of rare disease research to more common conditions.

References

1. Gordon G, Kearns L. Is the UDN N-of-1 enterprise ethically justifiable? *AMA J Ethics*. 2025;27(10):E737-E742.
2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. US Department of Health and Human Services. April 18, 1979. Accessed October 20, 2025. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html
3. National Institutes of Health. Diagnostic Centers of Excellence for the Undiagnosed Diseases Network (U01 clinical trial not allowed). US Department of Health and Human Services. Accessed October 20, 2025. https://grants.nih.gov/grants/guide/pa-files/PAR-23-289.html
4. Ramoni RB, Mulvihill JJ, Adams DR, et al. The Undiagnosed Diseases Network: accelerating discovery about health and disease. *Am J Hum Genet*. 2017;100(2):185-192.
5. Smith CIE, Bergman P, and Hagey DW. Estimating the number of diseases—the concept of rare, ultra-rare, and hyper-rare. *iScience*. 2022;25(8):104698.
6. Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. *Orphanet J Rare Dis*. 2022;17:163.
7. Splinter K, Adams DR, Bacino CA, et al. Effect of genetic diagnosis on patients with previously undiagnosed disease. *N Engl J Med*. 2018;379(22):2131-2139.
8. Cope H, Spillmann R, Rosenfeld JA, et al. Missed diagnoses: clinically relevant lessons learned through medical mysteries solved by the Undiagnosed Diseases Network. *Mol Genet Genomic Med*. 2020;8(10):e1397.
9. Schoch K, Esteves C, Bican A, et al. Clinical sites of the Undiagnosed Diseases Network: unique contributions to genomic medicine and science. *Genet Med*. 2021;23(2):259-271.
10. Yates J, Gutiérrez-Sacristán A, Jouhet V, et al. Finding commonalities in rare diseases through the Undiagnosed Diseases Network. *J Am Med Inform Assoc*. 2021;28(8):1694-1702.
11. Tan QKG, McConkie-Rosell A, Mahoney R, et al. Telehealth is effective in the evaluation of individuals with undiagnosed rare disorders: an Undiagnosed Diseases Network study. *Am J Med Genet A*. 2025;197(4):e63956.

The Undiagnosed Diseases Network is a research study funded by the National Institutes of Health to help both individual patients and families living with undiagnosed diseases and to contribute to the understanding of how the human body works.

Citation
AMA J Ethics. 2025;27(12):E876-878.

DOI
10.1001/amajethics.2025.876.

Acknowledgements
The Undiagnosed Diseases Network is supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health.

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

This article is the sole responsibility of the author(s) and does not necessarily represent the views of the National Institutes of Health. 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