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Is the UDN N-of-1 Enterprise Ethically Justifiable?

Gianna Gordon and Lisa Kearns, MS, MA

Abstract

The Undiagnosed Diseases Network is a national consortium of clinicians and researchers working to promote diagnostic research and accurately diagnose patients with rare diseases, many of whose conditions have long gone undiagnosed. This endeavor's importance should not, however, stop us from asking good ethics and policy questions about whether and when N-of-1 diagnostic research is justifiable. This article poses and considers questions about informed consent, information privacy, and justice in this very specific kind of human subjects research.

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Diagnostic Research

The Undiagnosed Diseases Network (UDN) is a research study funded by the National Institutes of Health (NIH) with a mission to help patients and their families end *diagnostic odysseys*, the time between symptom onset and accurate diagnosis. Founded as the Undiagnosed Diseases Program in 2008,[1] the enterprise has expanded twice: in 2013 it became a nationwide network renamed the UDN, and in 2023 it transitioned into a larger, self-sustained network that includes public and private partners.[2] Physicians can refer undiagnosed patients to UDN clinician-investigators and must provide extensive personal health information and patients' family health history. The network typically takes 6 to 8 weeks to make a decision about an application.[3] Once an adult or pediatric patient (hereafter, "patient") is accepted, the estimated length of time to arrive at a diagnosis ranges from 1 week to 4 years.[4] Approximately 30% of patients receive diagnoses from the UDN,[4] which is a low percentage relative to diagnostic success rates for more common diseases.[5]

The UDN collects patient data through individualized phenotyping and genomic data analysis and then compares that data against an existing database to reach a diagnosis.[6] While this kind of research process is used in large-scale cohort studies of diagnostic yield,[7] it is individualized in the UDN. For this reason, it has been compared to N-of-1 research[4]—in which an intervention is tested on one or a few patients—but with the patients themselves as the objects of study. The N-of-1 approach as a diagnostic

research tool is not widely employed because it is labor intensive and requires specialized expertise and significant funding.[8] Although the UDN has surmounted these hurdles, there are still important ethical questions about the diagnostic research enterprise itself, especially regarding the diversion of taxpayer-funded resources to efforts that benefit such a small population of patients. Below we review key ethics concerns, suggest potential ways to address them, and then discuss whether these solutions are sufficient to regard the UDN enterprise as a whole as ethically justifiable.

Ethics

Oversight. N-of-1 research requires extensive oversight of both patients and the process to ensure that diagnostic research is conducted fairly and transparently and that patients' well-being is safeguarded. As N-of-1 patients have such rare or unique conditions, additional precautions are necessary to ensure that the informed consent process is thorough and specific, that privacy protection capabilities are transparent, and that justice concerns about access and cost are addressed. But because the UDN uses a centralized institutional review board[1] to review procedures instead of the case-by-case review process typically used for human research participants,[9] patients might not be evaluated as fully as they should be, especially regarding consent processes. A more thorough review process at the UDN, however, would be unrealistic, given the substantial resources, time, and expertise necessary to evaluate patients on the scale of the UDN program, which had accepted 3308 participants as of July 2, 2025.[10] Due to the current uncertainty of continued funding for many NIH projects, the UDN's capacity for patient oversight presents a substantial challenge, and resources are not likely to be added.

Informed consent. A thorough informed consent process is essential to ensure that patients understand what N-of-1 research involves and to help them manage expectations about their role and what participation can achieve. However, this process is exceptionally challenging for patients with exceedingly rare—heretofore undiagnosed—conditions, whose circumstances, experiences, and goals vary. Upon acceptance, patients sign a consent form that reviews known potential risks of participating in the program and states that participants can withdraw without penalty, at any time. Yet, given the likely considerable diagnostic efforts already undertaken by patients and their families and the difficulty of being accepted into the UDN, patients might feel heightened pressure to continue participation. It is also important that participants understand their own role in the N-of-1 process, which could involve years of doctor's office or clinic visits, as well as the possibility that an accurate diagnosis might not be obtained, and, even if it is, that there might not be treatments available. That most patients with rare diseases are children intensifies these concerns significantly. Some parents or surrogates asked to consent on behalf of a child patient, for example, might find it emotionally difficult to assess risk, to refuse to subject their child to a substantial risk if there is a prospect of benefit, or to refuse steep financial burden to try to help their child with a rare disease.

Privacy. Protecting privacy can be a daunting task for an organization created to generate and disseminate data. The UDN shares data with other researchers to facilitate diagnoses, and though it uses encryption and limits external access, the ultra-rare symptoms of N-of-1 patients could make true anonymization difficult. Additionally, researchers might request family data, raising further privacy concerns, especially regarding findings of heritable conditions. Moreover, researchers' queries to one

platform used by the UDN are visible to other researchers, creating another potential threat to patient privacy and potentially even to current or future insurance coverage.[11]

Justice. Health care for very small patient populations is by its nature difficult to access due to the small number of knowledgeable clinicians and the resources needed to seek, undergo, and pay for care. Unsurprisingly, patients from underrepresented groups and under-resourced communities are frequently excluded from clinical research, as well as being unable to obtain care. Some members of these populations face logistical barriers to trials, others might not trust the medical research enterprise, and others simply might not be asked to participate.[12] This unequal representation applies to the UDN, where, as of 2024, the majority of applicants (approximately 70%) and accepted participants (65%) identified as non-Hispanic White.[13] Furthermore, the fact that the UDN clinical sites currently accepting new applications are in coastal cities or major metropolitan areas[5] means that the majority of potential participants are hundreds of miles or more away from access to its researchers.

Those fortunate enough to be referred to the UDN also face cost barriers. In the first 2 phases of the program, the UDN paid patient costs, but in phase 3, the NIH pays for research and third parties pay for "patient services."[14] These include clinical lab work, procedures, and imaging, which insurers might not cover, and this lack of coverage can affect some patients' ability to participate. Importantly, while the cost burden has shifted more to the patient in phase 3, the benefit has not: just 30% benefit from a diagnosis[4] while the UDN gets 100% of the benefit of the clinical data and research. It is also not clear whether the gap between decreased federal funds in phase 3 and the UDN's budget can be filled by outside entities, which could further affect patient costs. Even if commercial interest in the UDN could bridge the gap, it would raise serious concerns about conflicts of interest that must be considered should the UDN form public-private partnerships in the future.

Overall, although the UDN budget is small compared with that of other medical research programs, it still uses public funds for personalized health care, and public funds should benefit the greater population, not just an extremely small portion of that public—one that, moreover, does not accurately reflect the country's ethnic and racial composition.

Should the N-of-1 UDN Enterprise Exist?

There are advantages outside of diagnoses for members of extremely small populations that do benefit the greater population. The UDN had published 307 manuscripts on its findings as of July 2, 2025, helping create foundational knowledge upon which potential future treatments can be based.[10] Another benefit is that, even when their conditions were not diagnosed, participants have reported positive experiences, including increased access to medical care and the ruling out of certain conditions.[15] It is also important to keep in mind that the 30% of patients who receive diagnoses represent people, and often families, who had been struggling with illnesses with no explanation.

Despite benefits conferred by the UDN enterprise, concerns regarding patient oversight, informed consent, patient privacy, and equitable access persist and echo similar concerns about genetic interventions, research, and treatments for very small populations. There are steps that can be taken to mitigate, if not fix, these problems. First, the UDN should establish a dedicated oversight committee comprising members with relevant expertise in ultra-rare disease diagnosis and treatment and in genomics research, including pediatric specialists in these areas. The oversight committee could

provide valuable assistance in all aspects of consent and monitor potential conflicts of interest, should they arise. With appropriate expertise and with procedures and policies in place, the committee should be able to manage the volume of applicants.

UDN sites should also implement a continuous consent review process that provides updated information when available and allows participants to repeatedly reaffirm consent. Diagnostic success rates are crucial information for patients considering whether to continue in the program or pursue a different route and must be disclosed. Researchers must ensure that patients understand that, while a diagnosis is the goal, a diagnosis does not mean a treatment exists or that an existing treatment is accessible. The consent process should also stress that rare disease treatments can be exorbitantly expensive, grueling ordeals and might not be covered by insurance, which ultimately means that even a medically actionable diagnosis might not be actionable after all. Transparency about what can be done to protect privacy, including the impossibility of guaranteeing it, is essential, and researchers and clinicians must be absolutely clear on the ultimate purpose of patient data, how it is stored and shared, and which third parties would have access to it.

Given the state of access to health care in general in the United States, we are not optimistic that equity concerns regarding access to and cost of diagnostic assistance for marginalized groups within a minuscule portion of the population can be adequately addressed. Yet there are steps that can be taken now. Opening additional diagnostic centers in less populated areas and partnering with community agencies would help make underrepresented groups aware of the UDN's work. A 2024 study examining the UDN's effort to improve inclusion of marginalized groups noted laudable, but ultimately not successful, progress (due to language barriers and financial difficulties, for example) and suggested further improvements.[15] Charitable or patient organizations also could be enlisted to help manage attendant costs.

However, one justice concern is, in our minds, insurmountable: the use of substantial financial and human resources to benefit such small populations when diseases that affect hundreds of thousands of lives annually continue to lack adequate funding. One solution would be a greater reliance on philanthropic financing, which could be directed, without ethical conflict, to the UDN. Such a funding model has precedent in the n-Lorem Foundation,[16] which helps support treatment for patients with "nano-rare" diseases.

Conclusion

The diagnostic enterprise at the UDN exists in an ethical gray area: it offers individualized attention but possibly insufficient evaluation, federal funding but burdensome cost sharing to patients, and access for some but hurdles for many others. By using an N-of-1 approach as a diagnostic tool, the UDN takes research to a new level by providing individualized attention to patients with extremely rare diseases that defy the understanding of current medical practice. It goes without saying that the UDN enterprise is admirable and that, in light of the complexity of rare diseases, it has been successful in creating new foundational knowledge for the greater good. Furthermore, there are workable ways that the UDN can resolve the ethics concerns we have raised about oversight, informed consent, patient privacy, and equitable access. However, funding the UDN through taxpayer resources remains ethically insupportable. We find the enormous inequity in this specific justice concern sufficient to regard the UDN's current operating model as ethically indefensible, although philanthropic support could be one way to ameliorate taxpayer burden. Once philanthropic support has been

obtained, the UDN is ethically justified in moving forward with its important work and laudable goal of achieving a diagnosis for every person suffering from an extremely rare disease.

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Gianna Gordon 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. She will attend the University of Chicago in fall 2025 to study biological sciences and genetics. 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.

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