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FROM THE EDITOR

Equity and Ethics in the Undiagnosed Diseases Network

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The US Food and Drug Administration defines a rare disease as a disease or condition affecting fewer than 200 000 people in the United States.[1] However, many rare diseases only affect a handful of individuals, with most of those remaining undiagnosed—without a known cause or pathology, despite evaluation by clinicians. Altogether, the aggregate impact of rare diseases is immense, encompassing thousands of distinct conditions that affect between 25 and 30 million Americans.[2] Despite the number of people affected, the advancement of our diagnostic and therapeutic capabilities has often left patients with rare and undiagnosed diseases behind—such that they face diagnostic delay, limited access to specialized care, and few established treatment options.[2,3] This theme issue of the *AMA Journal of Ethics* investigates ethical and equity dimensions of that reality.

Technologies such as whole genome sequencing, RNA and protein analysis, and bioinformatics can reveal new insights into underlying disease pathology and have begun reshaping the diagnostic and treatment landscape with a promise of personalized medicine, at least for some.[4] However, industry application of these advancements often prioritizes conditions affecting broader populations to ensure profitability and market share, especially for specialty therapeutics.[5,6] Statutes like the Orphan Drug Act of 1983 were established to incentivize development of drugs for rare diseases.[5,6] However, this law can be exploited, as companies leverage orphan drug designation to gain market advantages, including extended patent protection, while also expanding into larger, more lucrative markets for non-orphan indications.[6] This dynamic underscores the need for thoughtful policies to ensure that these scientific advancements benefit all patient populations, including those with the rarest conditions, who would otherwise be left without a path forward.

The Undiagnosed Diseases Network (UDN) has sought to address some patients' unmet needs by providing a structured pathway for those with elusive conditions to seek diagnostic clarity. Started in 2008 as the Undiagnosed Diseases Program, the UDN is a federally funded research initiative with multiple clinical sites across the United States.[7,8] The UDN has formulated a team-based, multidisciplinary approach to solving select complex cases and exists to promote 2 goals: "1. To provide answers for patients and families affected by mysterious conditions, and 2. To learn more about rare and common diseases."[9] As of April 2025, the UDN had received 7879 applications, from which it accepted 3195 patients.[10] Evaluations have been completed for roughly 88% of

those patients, leading to diagnoses for 886 participants (32% of those with completed evaluations).[10] Even with these successes, the UDN operates within a limited capacity and is accessible to only a subset of patients, raising important questions about equity, accessibility, and the balance between research and patient care.[11] For patients with undiagnosed diseases, the allure of possible answers or treatment options can be strong, but the UDN does not guarantee either,[12,13] and thousands of patients are not accepted into the UDN at all. Without careful guidance and education from trusted clinicians, these patients are vulnerable to misinformation and unrealistic expectations.

This issue examines the nature and scope of ethics and equity responsibilities of clinicians, researchers, and policymakers in the diagnosis and care of patients with undiagnosed and rare diseases. While the UDN itself warrants examination, it is also a salient lens through which to consider the rapidly growing areas of precision and personalized medicine, genetic research, and advanced diagnostic technologies that affect patients generally, not just those with undiagnosed diseases. Clinicians continue to have a responsibility to support and care for patients, even those for whom there are no clear diagnoses or treatment protocols. The perspectives shared in this issue aim to explore what ethical, compassionate, and patient-centered care can and should look like in these complex and often uncertain circumstances.

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