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FROM THE EDITOR

Equity and Ethics in the Undiagnosed Diseases Network

Georgeann Booth and Peter Nelson, MD

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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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

What Are Ethical Merits and Drawbacks of Viewing "Medical Mysteries" as Human Subject Research?

Tom A. Doyle, PhD and Erin Conboy, MD

Abstract

Patient-subjects' participation in an Undiagnosed Diseases Network (UDN) protocol can afford access to innovative diagnostic techniques, especially in genomic medicine, which can shorten the time it takes to accurately diagnose a so-called "medical mystery." But UDN research processes can be complex and involve many variables, which can suggest to some patient-subjects that having enrolled in a UDN protocol was not worthwhile. This commentary on a case rife with diagnostic ambiguity offers a dynamic model of consent that can both facilitate prospective UDN patient-subjects' assessment of potential risks and benefits of participating in diagnostic research and be a source of community engagement.

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Case

G is a 28-year-old man who has always been told he was clumsy. When growing up, G hit all developmental milestones but suffered numerous fractures from falls. Although G has seen several neurologists, diagnostic workups have revealed no pathogenic genetic variants, and G has never received a diagnosis. G's lack of coordination has gotten worse, and he now uses a cane to try to avoid falling again. G sees another neurologist, Dr N, who suggests that G apply to participate in a research protocol in the Undiagnosed Diseases Network (UDN). With Dr N's help, G enrolls in a protocol at a site within driving distance of his home. UDN clinician-investigators perform whole genome sequencing and other screening tests that reveal that G has a variant in a gene known to cause neuromuscular problems.

The UDN coordinates a *C elegans* study, in which a genetic change analogous to G's is induced in the genome of a *C elegans* roundworm to examine, usually over 18 to 20 days, whether the modification induces a pathogenic or causative response. UDN investigators observe this response in the worm and conclude that G's variant is likely a pathogenic variant that causes his neurological symptoms (ie, lack of physical coordination). UDN clinician-investigators inform G that they plan to publish an article

detailing the diagnostic processes and outcomes they've learned from his participation in the UDN research protocol.

G feels somewhat satisfied to have an "answer" to the mystery of the origins of the neurological symptoms he has experienced all his life. G is disappointed to learn, however, that there is no treatment available to help mitigate his symptoms and wonders if it was worth all the effort and resources to go through the UDN research process.

Clinician as Detective

In a 2012 article featured in *The Lancet*, the Undiagnosed Diseases Program (UDP) at the National Institutes of Health (NIH) is described as something akin to "a television programme" in which "a team of physicians works to identify their patients' mysterious, life-threatening ailments."[1] This program would eventually expand into a network, the UDN, and the clinicians who worked on these cases would be compared to detectives; a recent article covering the continued work of the UDP invites the reader to "meet the NIH detectives cracking medicine's toughest cases."[2] This is an apt comparison, considering that many of the UDN participants have a complex array of symptoms that can most accurately be described as a medical mystery.

Fiction offers numerous examples of physicians who, in a eureka moment, suddenly solve a medical mystery by piecing together all the available evidence within their minds. However, the reality is that solving a medical mystery is an arduous process that requires the development and trialing of novel diagnostic techniques and technologies. G's case provides us with an example of this process, wherein the answer comes not in a eureka moment, but rather from the results of an experiment using an animal model made possible by the coordinated efforts of multiple clinician-researchers across the UDN. Yet such a demanding diagnostic process has the potential to result in a divergence of opinions: the answers that satisfy a research team might not be the answers that satisfy a research participant. Although G was provided with an answer that was compelling from a scientific point of view, he nevertheless feels personally dissatisfied with what this answer can do for him. Thus, while G's medical mystery might be "solved," he still wonders: Was it worth it? This commentary considers the ethics of trying to find answers to medical mysteries through human subject research and, specifically, the reality that what's found or remains unknown can feel unsatisfactory to some patient-subjects.

Patient and Subject

The Belmont Report, a foundational document that outlines ethical values that have informed federal regulations on ethical conduct concerning research involving human subjects, stipulates that clinical research should be treated as distinct from clinical care.[3] The reasoning for this distinction pertains to the differences in ethical duties ascribed to physicians and human subject researchers. A physician is ethically obligated to always act in the best interest of their patients, whereas a researcher's primary responsibility is to produce scientific and medical knowledge that has benefit for future patients or the general public. While researchers are ethically obligated to design and implement their protocols in a manner that minimizes harms to human subjects, it is beyond the scope of their obligations to design and conduct research that holds promise of, much less ensures, personal benefit to human subjects from participating in the research. Some have taken this lack of obligation to mean that "protecting participants is not the top priority in clinical research," since the production of generalizable

knowledge might or might not be at odds with research participants' best interest.[4] Contrary to this assertion, language in both the aforementioned Belmont Report and the federal policy based on it, known as the Common Rule,[5] indicates the importance of conducting a risk-benefit assessment in order to ensure that a protocol's anticipated risks do not exceed its expected benefits for both the general public and human research subjects. It should be noted that researchers are not discouraged from designing protocols that might benefit subjects, despite there being no obligation to do so.

While the Belmont Report emphasizes that human subject research is distinct from clinical care, the infinitesimal rarity of suspect pathogenic variants causing rare diseases often results in a thinning of the distinction between patient care and human subject research. One defining feature of clinical care is that its scope is limited to a single patient's well-being, but in UDN research it is not uncommon for a protocol to be individualized for a single human subject with a novel genetic variant. Such a narrow research scope invites confusion about UDN researchers' ethical obligations to their research subjects and thus about what patients can expect if they participate in research. Aptly, the term *medical mystery* itself implies individualization—a single case to be unraveled by the physician detective. Such individualization is certainly characteristic of G's case, as the *C elegans* study is an investigation into a genetic variant that might be unique to G's genome. Nevertheless, it is necessary to remain cognizant of the fact that UDN protocols pertain to research, and thus the ethical obligation of the clinician-investigator is confined to mitigating risk to human subjects and maximizing benefit to future patients rather than providing individual patients with a form of treatment.

While viewing medical mysteries as human subject research produces confusion about the ethical obligations of clinician-investigators and thus what patients can expect if they participate in research, attempting to solve medical mysteries through diagnostic research is not without its ethical merits. One such merit has to do with upholding distributive justice for undiagnosed patients. Once undiagnosed patients, like G, have expended diagnostic resources available to them in a clinical setting, are they any less deserving of a diagnosis? By treating undiagnosed disease as research, clinician-investigators provide the undiagnosed patient population with access to resources that would not be available or justifiable within the scope of usual clinical care. As G's case shows, candidates for UDN research have reached the outer limit of what can be provided in routine care, and thus the uniqueness of their cases precipitates the use of novel diagnostic techniques that more appropriately fall within the scope of research. Through the UDN, undiagnosed patients are given access to cutting-edge genetic diagnostic techniques, a nationwide network of clinician-investigators, and the potential for breakthroughs to occur though ongoing case-matching or genomic-wide association studies.[6,7,8]

The availability of these resources, made possible through participation in UDN research, has the potential to shorten the time to diagnosis and thereby mitigate harms associated with diagnostic delay. Estimates vary on how long it takes for patients with an undiagnosed disease to eventually obtain a diagnosis. Some studies indicate an overall average of 4 to 5 years,[9,10] whereas other studies have found that some patients might wait 20 years to receive a diagnosis.[11,12,13] During this period, undiagnosed patients and their caregivers face both the psychological distress of uncertainty and the financial distress of high health care utilization and spending.[14] Yet participation in the

UDN can result in greater diagnostic clarity and, potentially, a diagnosis for many patient-subjects. A retrospective analysis of UDN research found that, over a 4.5 year period, 231 of 791, or 29%, of patient-subjects received a diagnosis.[7] Such diagnostic clarity allows UDN patient-subjects to avoid the emotional stress and financial strain caused by unwarranted testing and unhelpful treatments that result from misdiagnoses.[15] Additionally, it is important to note that, without a diagnosis, patients will remain unaware of any clinical trials or potential therapies for their condition that aim to slow or abate disease progression.

Was It Worth It?

Qualitative investigations consistently report that undiagnosed patients and their caregivers emphasize the significance of finding "answers" about the diagnosis of their or their child's condition.[16,17,18] In one of these studies, it was found that participants indicated that the "search for answers" was the main motivator for participating in diagnostic research.[17] In another study, a parent of a UDN patient-subject reported participating in research because her child "deserves a chance at having answers or paving the way for answers for others."[16] These investigations point to the likelihood that many UDN subjects maintain hope that diagnostic research can help solve their or their child's medical mysteries. While it is unclear what G's original motivation was for agreeing to be a participant in UDN research, it is not unreasonable to assume that finding answers was a part of this motivation.

Although the motivation to find answers is shared by both the participant and the clinician-researcher, the potential for divergence between them with respect to what counts as an answer illuminates some of the ethical drawbacks associated with treating medical mysteries as research. In G's case, the medical mystery is considered solved by an answer that satisfies his research team. Despite having this answer, G nevertheless wonders if, in his case, such an involved research process was "worth it" just to get him this answer. This conclusion is ethically worrisome, as it is expected that, before participating, a research subject is able to make an informed decision as to whether the research protocol's overall purpose or goals is something they find worthwhile. It is an ethical requirement for potential research subjects to be provided with enough information about the research to make an informed decision or refusal to participate in such research.

Yet, in undiagnosed diseases research, wherein the ambiguity of a medical mystery might render research outcomes that are also ambiguous, it might not be possible at the time of initial consent to fully iterate the specific goals of the research protocol or the full scope of the burdens that might come with participating in the research. In G's case, at the time of initial consent it might not have been possible to convey that the purpose of the research was to conduct a *C elegans* study, much less the potential for this study to reveal the pathogenicity of G's symptoms. For this reason, it is not entirely surprising that G might have agreed to participate in UDN research without fully appreciating the study's purpose.

In addition to not understanding the study's purpose due to its ambiguity, G might not have fully understood the scope of the study procedures, as would be outlined in the initial study consent. Some studies report that research subjects often spend much of the informed consent process asking questions about the potential of genetic sequencing to find diagnostic answers rather than inquiring about key study details.[19,20] In consequence, many UDN patient-subjects leave the initial informed consent

discussion without adequately assessing whether participating in the research would be worthwhile. For the UDN specifically, it is important that research subjects be made aware that their biological samples and genetic data may be used in a wide array of projects, many of which do not actually pertain to providing them with a diagnosis. For example, samples and data gathered from UDN participants could be used to validate novel diagnostic methods that might be useful for future patients but provide no benefit to the research subjects themselves. Informing UDN patient-subjects of these procedures makes them aware that research that might seem insignificant to them could have an impact on the broader UDN community.

Thinking Dynamically and Finding Community

One potential way to address the ethical challenges discussed above is the implementation of a dynamic consent model. Given the uncertain and longitudinal nature of many UDN protocols, a form of broad consent is often required to allow future research to be conducted with samples and data obtained from subjects participating in the UDN. Dynamic consent, a form of broad consent, usually consists in providing subjects with a digital platform that enables them to keep up-to-date on how their samples or genomic data are being used as well as to decide whether they would like to participate in future studies.[21,22] The Rare UK Diseases of bone, joints, and blood vessels (RUDY) study is a leading example of an implementation of dynamic consent. A 2017 publication on the RUDY study explains how the platform affords researchers and research subjects the capability to engage in discussions about research findings and potential directions for future research and the capability for subjects to become informed about and reconsent to sub-studies, as well as to provide up-to-date information about their disease and its progression.[23]

If a dynamic consent platform were to be developed for UDN subjects, individual subjects like G would have the ability to keep up-to-date on the research conducted on their samples. Ideally, then, access to this platform would allow G not only to gain a better understanding of what research was being done to solve his medical mystery but also to decide if certain research was worthwhile from his point of view. However, it should be recognized that providing research subjects with granular control over their data and samples could have drawbacks, as having even a single UDN subject withdraw their data and samples could hinder scientific progress on rare disease diagnosis. Furthermore, establishing and maintaining a dynamic consent platform is resource intensive and would require significant coordination across UDN sites. As Grady and colleagues point out, providing research participants with greater agency often means an overall higher resource burden for institutions.[24] Additionally, it is important to acknowledge that dynamic consent should not be seen as a replacement for an informed consent process. When potential UDN study candidates are approached for enrollment, the initial informed consent discussion should describe the longitudinal nature of UDN research and also indicate how data and samples could be used for other purposes.

It should also be acknowledged that dynamic consent is not the only way for participants to become more engaged in the research being conducted at the UDN. The UDN Foundation manages and maintains the Participant Engagement and Empowerment Resource (PEER).[25] Through PEER, UDN participants can engage with one another to share information about various resources, provide social and emotional support, and discuss research being conducted at the UDN. If G had been made aware of PEER early in his UDN participation, it is possible that he would have found participating in UDN

research to be worthwhile in that it provided him with access to a community of those who also face the uncertainty of undiagnosed disease.

Additionally, by being a UDN participant, G could create a profile on MyGene2, a digital platform where individuals with undiagnosed and rare diseases can engage with clinicians, researchers, and other families or patients about their disease.[26] This engagement can help address the social isolation experienced by the undiagnosed community.[27] By being able to connect with others who might have the same or similar genetic variants, G might feel that finding the answer to his medical mystery is worthwhile insofar as it has allowed him to find others who might share a lived experience similar to his own. Before enrolling G in the UDN, then, it might have been worthwhile to provide him with preliminary or trial access to these communities so that he could get a better sense of what it means to participate in UDN research. This experience could have ultimately helped him decide if participating in the UDN would be "worth it."

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Editor's Note

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental. The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

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CASE AND COMMENTARY: PEER-REVIEWED ARTICLE

What Is the Nature and Scope of Physicians' Duties of Care to Patients Without a Diagnosis?

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Abstract

Patients whose conditions are undiagnosed face stress and limited, delayed access to interventions that address their specific needs. This commentary on a case describes key ethical values that tend to conflict when clinicians try to care for patients with undiagnosed conditions and underscores the need for equitable, precise care plans when the sources and causes of patients' illness experiences are yet unknown.

Case

L is 24 years old and has experienced severe pain, neuropathy, and periodic lower extremity weakness throughout her life. L now uses a wheelchair and receives Social Security Disability payments and Medicaid insurance.

L has seen several specialists and undergone extensive diagnostic testing over the last few years. Neuromuscular variant panels, muscle biopsies, and various clinical and research-use tests have not generated information that have helped L's physicians help them.

L recently asked Dr M to help them apply to be enrolled in an Undiagnosed Diseases Network (UDN) protocol. Dr M does not believe the UDN will help and is unsure about whether L has the financial resources, especially given that the closest UDN site is several hundred miles away. However, Dr M is concerned that not supporting L's application could exacerbate L's feelings of disappointment and hopelessness about finding the source of their illness experiences.

Commentary

As defined by the US Orphan Drug Act, a rare disease affects fewer than 1 in 1750 individuals, based on the current population of the United States.[1] However, while individually uncommon, the more than 7000 known rare disorders together affect over 300 million people worldwide.[2] As the large majority of these conditions has a genetic origin,[2] obtaining a specific molecular diagnosis can be life-changing for these individuals, as it can (1) provide a clearer understanding of current symptoms, future risks, and long-term prognosis; (2) allow for the discontinuation of ineffective treatments and the initiation of

more effective therapies and targeted surveillance; and (3) facilitate cascade screening of family members, as well as inform reproductive counseling.[3]

Over the past 30 years, a revolution in molecular diagnostics has increased the diagnostic rate of clinical genomic analyses from 3% to 5% (karyotype alone) to 30% to 50% (exome or short-read genome sequencing).[4,5,6] This dramatic increase has changed the practice of clinical genetics and improved the lives of thousands of affected Americans each year. However, most rare genetic disease patients are like L. Despite clinicians' best efforts, use of the latest clinical diagnostics, and a costly diagnostic process, they remain without a diagnosis.[7]

In the United States, L and the millions of other undiagnosed individuals constitute the largest single fraction of rare disease patients.[8] These individuals and their families face unique challenges, including psychological stresses from the uncertainty of their condition, long periods of inconclusive testing and consultations, and a lack of understanding from family members, friends, and their local communities. They might also struggle to connect with disease-specific support groups, experience barriers to accessing needed services, and face the very real risk of medical abandonment.[9,10,11] Risk of abandonment is particularly relevant to L's situation, as it would appear that contemporary medicine has had few answers for L despite prolonged and invasive diagnostic testing. At this point, L's physician, Dr M, acknowledges L's psychological burden of being undiagnosed but is unsure whether an evaluation by the UDN would be in L's best interests. This case highlights the ethical challenges faced by clinicians who take care of patients with undiagnosed but suspected genetic disorders and illustrates the potential tensions between the ethical principles guiding clinical practice, which prioritizes the best interests of the patient, and clinical research, which prioritizes benefits to society.

The Undiagnosed Diseases Network

The UDN is a research program funded by the National Institutes of Health that is designed to improve the diagnosis of rare and undiagnosed conditions and discover the disease mechanisms associated with these conditions.[12,13] It currently has 24 clinical sites in 20 states[14] that serve as test beds for a variety of research activities, including discovering new disease genes, advancing our understanding of the molecular pathology of genetic disorders, and improving the technology used for genetic analyses. Because UDN sites are designed to provide molecular diagnoses, they also can play a key role in the care of rare disease patients. However, this role is limited: a typical UDN site focuses on diagnostics and genomic pathology, not clinical management. Because providing ongoing care is typically out of scope for UDN sites, they are best viewed as one part of a broader, comprehensive approach to the care of rare disease patients, such as what can be offered by the National Organization for Rare Disorders Rare Diseases Centers of Excellence. In the case of a patient whose diagnostic evaluation is beyond the expertise of the physician, there is an obligation to consider referrals to specialists and clinics that have a realistic chance of making a diagnosis, including clinical research programs such as the UDN.

Physicians' Duties to Undiagnosed Patients

As a practical manifestation of the obligation to act in the best interest of the patient, physicians have a duty of care for their patients. Importantly, while diagnosing the underlying cause(s) of a patient's medical issues is a core function of health care, the duty of care is independent of the patient having an established diagnosis, as a lack of a

diagnosis does not prevent physicians from providing valuable care to their patient or referring their patient to specialists when they cannot provide such care themselves.

Given L's clinical course, Dr M is appropriately concerned about the potential psychological harm and financial expense of an unsuccessful UDN evaluation, as most UDN participants do not receive a definitive diagnosis.[15] In that regard, the duty of care also obliges physicians to have frank conversations about the current limitations of medical practice and research so that their patients can make informed decisions about their care.

A goal of these conversations is to cooperatively devise an optimal care strategy, one that prioritizes the needs and preferences of the patient while minimizing potential harms. In this case, finding the balance between L's preference to enroll in a UDN protocol and the potential harm of supporting (or declining to support) L's application can be particularly challenging, given the uncertainty and emotional burden experienced by the patient and inherent in their care. On one hand, Dr M can honor L's preference, as the UDN sites offer state-of-the-art diagnostic testing for rare genetic disorders. However, on the other hand, their scope is narrow, as they prioritize conditions with a high likelihood of being identified through advanced "omic" technologies, and few rare genetic disorders currently have targeted therapies or are "curable."[16] Patients without strong indications of benefiting from a molecular diagnosis with limited clinical actionability might face emotional distress and financial strain from pursuing evaluations that are unlikely to provide answers they need and desire.[17] Additionally, according to the American Medical Association *Code of Medical Ethics*, physicians are not obligated to provide care if the requested intervention is unlikely to benefit the patient.[18] However, physicians must still support patients' informed choices by clearly communicating potential risks, expected outcomes, and reasonable alternatives while respecting patients' values and goals.

In this case, redirecting L to other resources, such as pain management specialists or psychosocial support services, might align better with L's priorities and needs than a referral to a distant UDN site. Offering alternative strategies for managing L's condition can help preserve trust and mitigate feelings of hopelessness.[17] Moreover, Dr M's concern about L's financial limitations underscores another important aspect of minimizing harm. Supporting L's application to the UDN, knowing that travel and its associated costs might impose significant stress, risks exacerbating L's challenges and calls for a nuanced approach: directing L toward resources likely to provide tangible support, while addressing their hope for answers in a compassionate manner and clearly stating that choosing one path might exclude the possibility that another path might provide a hope of a diagnosis. Balancing these considerations would protect L's well-being and respect the limitations of existing medical expertise.

Shared Decision-Making

Dr M should actively involve L in decision-making[19] by discussing the UDN's purpose, scope, and likelihood of identifying a diagnosis, as well as the implications of receiving or not receiving a diagnosis.[20] L should also be informed of the UDN referral process, the UDN's limited resources, and potential challenges, such as the time and financial commitments, emotional toll, privacy concerns, and the possibility of uncertain or unexpected results. Furthermore, Dr M should offer expert guidance on what is known scientifically about L's symptoms while valuing L's lived experience, recognizing that patients are often the best experts on their own symptoms.

If Dr M determines that a referral is not appropriate, they should provide transparent reasoning, discuss alternatives, and ensure that L feels heard and valued.[21] Additionally, Dr M should acknowledge L's frustration and hardship in navigating the medical system thus far, which might contribute to feelings of powerlessness and distrust. By fostering trust and empowering L to advocate for themselves, Dr M can help rebuild confidence in the medical process.[22]

Finally, L's personal values and beliefs should be taken into account when considering the decision to pursue a diagnosis. For instance, while some patients prioritize the diagnostic process itself, others may view it as a path to treatment. Similarly, while some embrace genetic testing, others may have concerns about its potential implications. In addition to listening, Dr M must communicate with respect and empathy, avoiding paternalistic decision-making that disregards L's preferences.[23]

Tension Between Best Interests and Social Need

It is important to note that, while UDN sites are able to provide diagnoses for some patients, UDN sites are research centers with finite resources. As such, they operate under their own ethical framework, wherein advancing understanding of disease is an ethical principle that takes priority over delivering patient care.[24] Consequently, the scientific goals of the UDN take priority over diagnosing an individual patient when selecting participants. Referred patients are evaluated by committees that prioritize patients based on the likelihood of diagnosing their condition and the potential for discovering new genes or mechanisms of disease, not the severity of their disease or potential benefit of obtaining a diagnosis.[25] As this principle of research ethics privileges societal needs, it can create tension with the ethical principle of beneficence, with its focus on the individual patient.

The limited availability of UDN slots requires that Dr M consider, in collaboration with L, whether a referral would be a just use of this scarce resource or if others with greater needs might benefit more. The decision-making process of whether to offer L a referral should be transparent and must be free from bias related to socioeconomic status, race, ethnicity, gender, geographic location, or other factors. Dr M should also ensure that considerations such as L's engagement level, interest in or knowledge of genetics, or financial means do not unfairly influence a decision. In general, when discussing the possibility of referral, physicians should prioritize patients most likely to benefit from a UDN evaluation, possibly seek formal advice from the UDN as to additional clinical workups that might precede a UDN referral and evaluation, and not refer patients whose conditions could be diagnosed through standard clinical workups.[26]

In contributing to the fair distribution of scarce health care resources, Dr M should also recognize and address systemic barriers that might prevent underserved populations from accessing UDN services. Patients in rural areas, those facing financial difficulties, and those with language or health literacy barriers might struggle to navigate the referral process. If L decides that she wants, and Dr M agrees to, a referral, Dr M should help L overcome these barriers by identifying funding resources, walking through the referral process, or using translation services when necessary.[27] Physicians also need tools and institutional support to recognize and address these barriers, such as streamlined referral pathways and team-based care models that incorporate social workers and patient navigators. To mitigate bias and ensure accountability in how limited resources are allocated, the UDN has established a comprehensive manual of operations.[25] This manual details clear and consistent criteria for patient selection and for communication

with patients and families regarding the rationale for referral acceptance or denial, which further promotes transparency and equity.

Conclusion

We have summarized ethical considerations in Dr M's approach to L's case. The application of ethical principles is not straightforward, however, as these can conflict with each other, and there might be other issues to consider that require a careful weighing of multiple priorities in the course of shared decision-making. Cases of patients without a diagnosis, like L, can raise unique challenges for applying ethical principles.[16] In addition, new ethical considerations arise in considering a patient entering the research realm of the UDN, such as resource allocation and how to balance individual patient needs with the scientific goals of research. Even as science continues to advance at a rapid pace, thus improving the diagnostic and treatment capabilities of physicians, ethics remains at the foundation of clinical care to ensure the delivery of high-quality, patient-centered care.

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MEDICAL EDUCATION: PEER-REVIEWED ARTICLE

How Should Students and Trainees Be Taught to Support Patients With Undiagnosed Conditions?

Mylynda B. Massart, MD, PhD and Erika N. Dreikorn, PhD

Abstract

Patients with undiagnosed conditions often experience frustration and lose trust in health care. This article suggests how faculty in academic health centers can prepare their students and trainees to respond with care to the vulnerabilities and needs of patients seeking accurate diagnoses. Specifically, this article suggests the importance of clinicians' roles in validating patients' knowledge claims about their illness experiences. Such validation during clinical encounters can happen when clinicians prioritize symptom management, acknowledge uncertainty as an emotionally painful part of a patient's illness experiences, articulate limitations of clinical knowledge, and express values such as care, partnership, and compassion in their relationships with patients.

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Finding Diagnoses

When caring for patients with chronic, undiagnosed conditions, the first author (M.B.M.) has learned 2 challenging but essential lessons: how to live with the limits of science and medicine and how to be a caregiver when certainty is out of reach. Medicine trains us to collect facts, assemble data, make a diagnosis, and design a treatment plan. But what happens when that sequence breaks down? When the facts are unclear, the data incomplete, and the diagnosis elusive, how do we continue to confidently care for our patients? Early in her training, M.B.M. believed that if she read enough textbooks, attended enough lectures, and reviewed enough journal articles, she could overcome this uncertainty. But, instead, she has found the edge of what we know. Medicine is incomplete; science is imperfect. Despite how far we have come, despite remarkable advances in technology, artificial intelligence (AI), big data, and precision medicine, we are still limited in fully understanding the masterful complexity of human health. While AI will bring more facts to our fingertips than ever before, the true distinction between AI and physicians will always be the art of medicine—the human act of caregiving itself, which is what called M.B.M. to this profession in the first place. And so, as M.B.M. pursues answers as relentlessly as her patients seek them, she also wrestles with how

to be the caregiver they need today, even when certainty is just beyond her grasp. This is the tension—and the beauty—that drives both the scientist and the clinician within her.

Patients with undiagnosed conditions often have extensive clinical experiences characterized by inconclusive testing, specialist consultations, and many unanswered questions. When we health professionals find that evidence to support a diagnosis is absent or murky at best, we do not question the scientific process or our diagnostic tools. Instead, we diagnose the patient with anxiety, or we conclude that their obesity is causing "functional" symptoms that do not fit nicely into our algorithmic and evidence-based boxes. Perhaps we conclude that the patient does not match our specific "-ology" and should go see a different "-ologist" instead, as they might be a better fit for the black boxes over there.

These experiences leave patients feeling blamed or shamed for their own unanswered health questions as they travel to the next clinician and the next. Of course, patients will have anxiety about what is unknown, and this anxiety can morph into trepidation about the next consultation: Will the physician listen, or will it be another unsatisfying experience? Eventually, patients will feel gaslit, and they could be accused of "doctor shopping." If their symptoms involve pain, they might be viewed as drug seekers, further compounding the blame and shame they experience. Many will give up and fall into an abyss of disillusionment. In the modern era of digital access, patients often become their own physician-scientists, scouring the internet for answers and finding solidarity in their shared experiences. They must jump hurdles of information and misinformation available to everyone now on the internet. When patients share with their physician a potential solution that they have found and wish to explore, physicians often feel burdened by this additional and seemingly extraneous information.

Adapting Curricula

To achieve better care of patients with undiagnosed conditions, the authors propose 3 adaptations of medical education. Educators must teach physicians to (1) understand that medicine and science are not perfect, (2) validate patients' experiences and partner with patients in their medical journeys, and (3) use their knowledge and skills to manage symptoms when they cannot make a diagnosis.

Traditional medical training emphasizes definitive diagnoses and treatment plans yet lacks focus on managing uncertainty. By its very nature, medicine is not an exact science, and its limitations are often overlooked or poorly understood. M.B.M. remembers being told by educators in medical school that 50% of what they are teaching is wrong, but they don't know which 50%. Clinicians are not taught to recognize the imperfections of medical science or how to handle situations in which no diagnosis can be made. In her medical career, M.B.M. has seen long-held beliefs within evidence-based medicine reversed and watched as the profession changed course. Simultaneously, medical school curricula have evolved significantly to emphasize humility, empathy, and effective communication, thereby equipping future physicians with clinical communication skills. However, failure to implement these skills is still apparent when physicians care for patients who have unknown conditions.

To help physicians succeed, we medical educators must continue to take their curricula to the next level. Medical students and residents need to practice applying empathy and communication skills in a more formal manner, while simultaneously acknowledging the unknown in science and medicine. We must teach future doctors how to explain the

limitations of current medical diagnostics to patients and how to approach caregiving in the absence of a clear diagnosis and treatment plan. Students can practice validating a patient's experience and acknowledging the patient's journey and frustration. M.B.M. has found that doing so only takes a simple sentence: "I agree that something is going on with your health, and I hope we can get to the bottom of these symptoms, provide a diagnosis, or at least start managing the symptoms to optimize your quality of life." Frequently, she will tell patients that "while science and medicine may not have all the answers yet, we can still do our best to eliminate many of the possible causes and then focus on symptom management." While this approach can be implemented with standardized patients, the authors encourage medical schools to bring in more real patients to share their stories with students. The students will remember these stories long beyond their lectures on anatomy or biochemistry. During the clerkship years, educators should encourage students to take their time and learn from patients, instead of rushing through to meet the busy demands of clinical schedules. Clerkship should be a time for medical students to have the luxury of really listening to and learning from patients. This is a luxury they will not have in the future, and it is the perfect time for them to practice these skills. In M.B.M.'s experience, students given this experience and time will often learn valuable information that helps M.B.M. take better care of her patients.

Medical education can also train students to recognize and accept the limitations of medical science. Physicians must understand that uncertainty is not a reflection of their own competence; it is a reality of practicing in a continually evolving field. Once medical students face the imperfection of their future craft and recognize that medicine and science are incomplete, they then need to learn how to explain these limitations to patients in a way that builds confidence in their medical skill set without reflecting negatively on themselves. "Not having all the answers" is not a reflection of personal failure. We physicians are experts at finding information if it exists, but there are some cases in which the necessary information just does not exist. When we see patients and work with them, we must prepare them for uncertainty ahead, knowing that we won't always find the answers. If we do not set these expectations, patients will continue to seek specialist after specialist, hoping to check every unturned stone to find their missing answers. This is the actual failure: our feeding into and propagating a futile cycle.

Patient Collaborators

With these skills, we can better collaborate with patients. We can apply our empathy and communication skills to recognize patients as persons needing support and validation, even without a clear diagnosis. M.B.M. has repeatedly heard from patients that they just want to be seen and heard. This approach shifts the physician's role from "fixing" patients to bearing witness to their lived experience and championing their understanding and comfort. We can reassure our patients that we see and hear them, that we are still their caregivers, and that we will support them by prioritizing symptom management. We can learn from and apply the principles of palliative care in these scenarios, emphasizing pain and symptom management, emotional and spiritual support, and overall optimizing of quality-of-life goals. When we don't have all the answers, we still have many tools. These tools will range from treatment to management, depending on the symptoms. Our tools can significantly alleviate the physical and emotional suffering that accompanies a long diagnostic odyssey. We can support our patients through advocacy: assisting with accommodations at work or school and with paperwork to document the impact of their illness or symptoms on daily

functioning or to help them access supportive care resources that might be challenging to obtain in the absence of a diagnosis. We can also encourage our patients to participate in research and contribute to a scientific knowledge base that could one day help other patients. Ultimately, everyone wants answers. Applying our tools as best we can while managing symptoms reinforces the care given to our patients and eases their journey.

Until we can fully realize the vision of understanding all human diseases, we can learn how to tell patients "I don't know," while validating their lived experience and partnering with them to access support and manage their symptoms. We can train future physicians to manage the dual responsibility of recognizing the limits of medical science while delivering compassionate care. By doing so, we can transform the patient's journey from one marked by frustration and isolation into one rooted in hope and partnership, thereby ensuring that no patient is left behind due to the boundaries of current medical knowledge.

Mylynda B. Massart, MD, PhD is a family medicine physician in the Primary Care Precision Medicine Clinic at the University of Pittsburgh School of Medicine and UPMC in Pennsylvania. Her clinical practice focuses on patients with complex, often undiagnosed, conditions, many of whom have felt misunderstood or stigmatized. Her research interests include precision medicine, the integration of genomics into primary care, centering community and patient lived experience in research, and improving patient experiences in navigating diagnostic uncertainty.

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STATE OF THE ART AND SCIENCE: PEER-REVIEWED ARTICLE

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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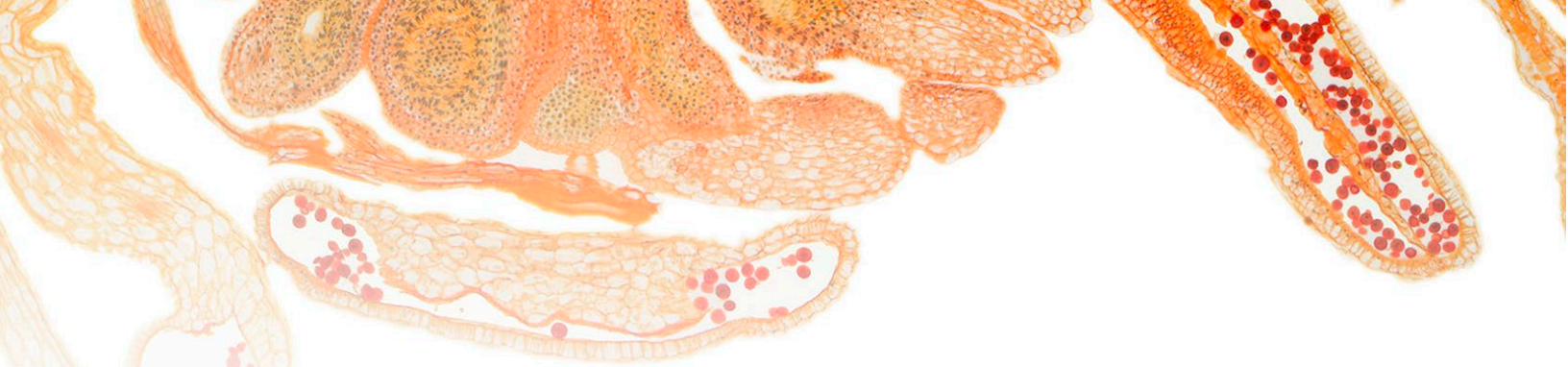

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POLICY FORUM: PEER-REVIEWED ARTICLE

What Should Be Roles of Industry and the Public in Diagnostic Research?

Barbara K. Redman, PhD, MBE

Abstract

Despite legislative attention from Congress in the 1980s, diagnostic research on rare diseases is not lucrative enough to garner sufficient private funding. The Undiagnosed Diseases Network supports diagnostic research and intervention innovation for patients with undiagnosed or rare conditions. This article considers structural conflict endemic among values seen as promoting corporate fiscal policy (eg, investment return, market share dominance) and values traditionally seen as motivating good public health policy (eg, rescue, non-abandonment). It argues that taxpayer investment in pharmaceutical innovation should be protected by expanding public understanding of conflicts of interest.

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Incentivizing US Drug Development

Even though markets can be shaped to produce common good, current drug development policy heavily supports public investments in private companies, making companies with high profit margins rich but restricting access to government-subsidized, privately produced drugs.[1] Limited access to pharmaceuticals is especially true of those with rare diseases, both undiagnosed and misdiagnosed, for whom the basic knowledge of etiology and resources necessary for diagnosis are not being produced. Profit-making values are infused into pharmaceutical companies, research funding priorities, and regulatory policy, leaving groups whose health issues do not accord these values undiagnosed and untreated in significant numbers. It is therefore important to accurately assess the degree to which public resources may be unfairly subsidizing commercial entities.

Other institutional forms (eg, public benefit corporations) or practices (eg, negotiating licensing agreements that include required access) could be adopted to increase therapeutics' accessibility and affordability.[2] One such effort to sustain academic centers' access to noncommercialized genetically modified cell therapies for rare diseases would use expanded access protocols and also allow for cost recovery.[3] A more far-reaching alternative is to reject the notion that the public sector's role is to fill the gaps created by markets and to require the economy to serve health.[4] This article calls

for equitable accounting of public research contributions for development of rare disease diagnostics and therapies.

Current US Drug Development Policy

The Bayh-Dole Act (BDA) of 1980 empowers universities, nonprofits, research institutes, and businesses to own and commercialize inventions funded by federal programs.[5] Yet the BDA could be said to be insufficiently protective of taxpayers' interests for several reasons. First, it focuses on applied research rather than on the largely publicly financed basic research necessary for downstream study and product development.[5] In addition, government research support is underreported in patents,[6] including those related to diagnostics, thereby limiting potential public health and safety benefits. And, more generally, a recent review concludes that measures to link public investment to pharmaceutical prices (eg, through Medicare price negotiations) have been implemented without accurate, transparent tracking of government pharmaceutical investment and with little effective oversight[7] and thus do not effectively incentivize diagnostic research for rare disease.

The Orphan Drug Act (ODA), now 42 years old, has been helpful but insufficient in incentivizing the development of drugs for many rare diseases, which the ODA generally defines as those affecting fewer than 200 000 Americans or more than 200 000 Americans if the cost of developing a drug for the disease cannot be expected to be recouped from US sales of the drug.[8] The reason for this failure is that the ODA includes incentives beneficial to sponsors who develop drugs for rare diseases that are also approved for more common conditions and could be developed without ODA incentives.[8] One could conclude that the ODA has been "gamed" and should be rewritten to assure that it actually supports rare disease research.

Pension and state funds also support biomedical research and development. While investors of this money have a fiduciary responsibility to act in the best interests of the savers, ironically, the diagnostics and therapeutics so produced might not be available to them because of cost.[9]

What work is being done to ameliorate this distortion of incentives? Few alternative structures have been tried and tested. Against this policy background, patients, clinician-investigators, and institutions supporting their work in the undiagnosed disease space face greater quality-of-care and ethical risks, in part because current policy is insufficiently protective of the public's investment. However, a recent National Academies of Sciences, Engineering, and Medicine report has considered regulatory improvements to advance rare disease diagnosis and treatment, including allowing many kinds of available data collected outside of randomized clinical trials— such as natural history data, registry data, real-world evidence, patient-reported outcomes, and data from open label extension studies—to be "used as supplementary, alternative and/or confirmatory evidence in support of regulatory submission and review of a drug product."[10] The report also cites an ethical obligation for the US Food and Drug Administration to share relevant information on the review and approval of drugs and diagnostics to treat rare diseases.[10]

Alternatives

Alternative approaches to incentivizing rare drug development that support public values and address issues of justice are available. A view from business ethics is that structural problems, including those affecting health, require collective and collaborative

approaches to ameliorate. Corporate legitimacy thus must increasingly be conceptualized as requiring collective effort in working toward resolution of structural problems, no matter who caused them, with the understanding that individuals face limitations in correcting the problem. On this view, profits are an instrument to fulfill corporate purpose rather than the actual purpose itself.[11] More in the public realm is the United Nations Convention on the Rights of the Child, adopted in 1989.[12] Since many rare and undiagnosed diseases occur in children, rights addressed or implied in this document—the right to advocacy and support, the right to health care, and the right to global effort to realize the goal of upholding children's rights[12]—are relevant to incentivizing rare drug development.

Broader frameworks with patient-centric values can also provide perspective on overcoming structural problems that impede access to new drugs. The Responsible Research and Innovation framework differs from current practice in considering societal engagement in research and innovation to be an early, permanent, and continuous endeavor as a means of ensuring that innovation processes are aligned with fundamental societal values.[13] Especially important is framing of the issue at stake by moving away from the neoliberal perspective of innovation and growth as the end good in itself toward consideration of broader impacts and values.[13]

Recent extensions of the concept of conflict of interest (COI) are also helpful in protecting public investment in drug development. Recall that a widely accepted definition of COI was first summarized for the medical community in 1993 as "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."[14] COI has primarily been applied to individuals with financial interests. Public-private partnerships, widely championed by governments to further economic goals, risk the public partner's interests through the private partner's institutional conflict of interest, such as when basic science contributions of the public partner are not adequately acknowledged.[15] Also relevant is the newly defined concept of structural conflict of interest—a set of conditions in which the primary interest of one sector (eg, health) is unduly influenced by the interests of another sector (eg, commercial) with different and often conflicting values.[15] Mitigating structural COIs requires policy revision that protects public interests,[15] such as by amending the BDA to better acknowledge contributions of publicly funded basic research.

How have these institutional and structural COIs been addressed? In the mid-1990s, demand for access to HIV therapies led pharmaceutical companies and their trade group to begin to attend to questions of access. A few initiated opening access to their already-approved products through philanthropic or other programs.[16] Importantly, the response to public pressure did not appear to extend to developing diagnostics and therapies and keeping them available for diseases that would not eventually be profitable. Why might that be the case? Sparke and Williams suggest that the power of pharmaceutical companies during the COVID-19 pandemic arose from structural cartelization among the companies and state authorities, which privilege economic growth, and philanthropies, which amassed their resources through pursuit of these same values.[17] Sparke and Williams label this situation as collusion, with nested, overlapping, and deeply networked relationships that enforce monopoly power. States invest in the basic and applied science that is freely available to firms and that reduces the risks of corporate product development[17] without consideration of public health

values. One could conclude that these structural issues are reflected in the public policies reviewed above, which have largely failed to protect the public investment in rare disease diagnostics and treatments.

Improving Diagnostic Research

Since most pharmaceutical research and development relies heavily on fundamental research from the knowledge commons, recalibration of benefits to better favor public interest seems justified. In a step in that direction, Modi and colleagues note that American and European pharmaceutical manufacturers and industries have made a commitment to share participant-level data and study-level data and protocols from clinical trials, provide public access to clinical study reports, establish public web pages displaying company data sharing policies, and publish results of all phase 3 clinical trials.[18] While "no US or EU [European Union] regulations currently mandate participant-level data sharing from industry-sponsored medicine trials,"[18] the companies should be pressed to uphold this agreed-upon commitment.

For undiagnosed diseases networks, there is an important obligation to construct a specialized infrastructure that includes standard definitions, data codes for medical records, network access to expert clinicians, evidence-based clinical practice guidelines, and globally coordinated diagnosis and research infrastructure so as to optimize access to clinical trials, prevent ineffective treatment, and take advantage of therapeutic windows. While artificial intelligence and digital tools to consistently reevaluate undiagnosed disease are under development,[19,20,21] the paucity of economic evaluations of rare disease diagnosis and treatment, including of cost-of-illness burden for patients and families, is unacceptable because it obscures real risks to patients and families.[22] Because rare diseases are geographically dispersed, the Undiagnosed Diseases Network International—a partnership among clinicians, researchers, and patient organizations—which launched in 2014 to help fill gaps impeding diagnosis for rare diseases,[23] is in a strong position to address the inequities addressed in this commentary.

Finally, bioethics literature highlights the necessity of self-advocacy to access clinical diagnosis and care and motivate public interest in advancing research relating to rare conditions. However, there is inequity among rare disease groups' self-advocacy capacity, as some do not have the educational, financial, or social resources to move their cause forward.[24] In part, this unjust situation reflects a poorly coordinated approach to rare disease at the federal level and failure of the health care system to provide opportunity for persons with rare diseases to participate in agenda-priority setting. Such a situation increases risks, reduces quality, and increases costs of care, as well as presenting ethical challenges for patients, families, clinicians, investigators, and the institutions in which care is provided and research produced. Petrov[25] has noted that every health care system must weigh rescue and non-abandonment for sick persons against using resources to promote population welfare. Although no one normative moral theory settles the conflict and societies vary in their views of an appropriate balance,[25] health systems must address it.

Conclusion

Current US policy does not protect public investment in research that should benefit persons with diseases that are not profitable. Regulatory frameworks could be amended to properly recognize the contribution of publicly funded basic research. Several value frameworks urge stronger patient involvement in priority setting and access to

resources. Because rare diseases occur around the world, research and clinical services must be global, supported by an infrastructure of data and expertise. Effective and safe diagnosis and treatment, free of stigmatization and disbelief, should be available for these patients—irrespective of their condition's rarity. Lack of interest or investment[26] is not acceptable. Ng et al state: "[W]hile no country has effectively addressed the challenge of financing rare diseases, the majority have clearly acknowledged that fairness of access is a moral obligation of public health systems."[27]

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MEDICINE AND SOCIETY: PEER-REVIEWED ARTICLE

According to Which Criteria Should the Undiagnosed Diseases Network's Value Be Assessed?

Meghan Halley, PhD, MPH and Holly Tabor, PhD

Abstract

The Undiagnosed Diseases Network (UDN) exists at an intersection of diagnostic research and clinical care and has 2 main goals: to advance diagnostic science and to facilitate accurate diagnoses in individual patient-participants with rare conditions or so-called "medical mysteries." The value of the UDN's translational research and clinical application model and of the results it produces derive from whether and to what extent the UDN achieves its 2 goals. This article considers criteria currently used to assess achievement of those goals, identifies their merits and drawbacks, and offers strategies by which the UDN might further advance diagnostic science and individual patient-participants' interests.

Origins of the Undiagnosed Diseases Network

The Undiagnosed Diseases Network (UDN) has always been unique in its stated goals and approach to scientific inquiry. Conceived within the National Institutes of Health in 2008 in response to patient demand and expanded to a national clinical research network in 2013,[1] the UDN describes its goal as "to both help individual patients and families living with the burden of undiagnosed diseases, and contribute to the understanding of how the human body works."[2] This focus drives the case-based approach utilized by the network, in which each individual patient receives a tailored evaluation based on the specific characteristics of their case, and scientific advancement comes from discoveries made through in-depth examination of each case.

Based on its stated goals, the UDN arguably offers an ideal model for ethical translational genomics research. The emphasis of the network on return of results speaks to a commitment to maximize benefits for research participants while simultaneously providing benefits to society in the form of generalizable knowledge gained for examination of rare disease manifestations. However, knowing the extent to which the UDN is achieving its goals—and maximizing its value—requires a critical examination of how the network evaluates its success. In this paper, we first examine the ways in which value has been measured within the UDN thus far. We then explore metrics that could be used to define and measure the value of the UDN. Finally, we

suggest an alternative approach that would measure value both short- and long-term and discuss the implications of such an approach.

Criteria

Metrics currently used to evaluate the UDN take multiple forms. The Table provides an overview of the types of metrics tracked and examples of each. The UDN Data Management and Coordinating Center (DMCC) tracks and publishes multiple metrics related to the application and evaluation process, the number of diagnoses identified, and scientific products, including manuscripts published and genetic variants and records shared in public databases.[3]

Table. Summary of Currently Collected UDN Metrics

Category	Key metrics
Application and evaluation process	• Number of applications received • Number of participants accepted • Number of evaluations completed • Number of diagnoses identified
Characteristics of identified diagnoses	• Certainty of diagnosis (ie, certain, highly likely, tentative, low) • Chief method of identification (eg, exome sequencing, directed clinical testing) • Knowledge of mechanism (ie, yes, no, other) • Timing and source of diagnosis (eg, during application review, after evaluation) • Importance of diagnosis for future management of patient and family health (ie, major role, some role, no role, other) • Available treatments for diagnosis (ie, yes, no)
Scientific products	• Number of manuscripts published • Number of patient records and genetic variants shared
Patient experience	• Satisfaction with participation

Undiagnosed Diseases Network.[3,4]
Abbreviation: UDN, Undiagnosed Diseases Network.

As described in its *Manual of Operations*, the lead clinical site also assesses specific characteristics of each diagnosis it identifies.[4] This information is submitted to the internal, shared network database and was last reported for the network in a manuscript published in 2018.[5] The DMCC also distributes follow-up surveys to participants after their UDN evaluation to assess their satisfaction with participation, although this information has not been published or shared publicly to our knowledge.[4]

Gaps

Currently utilized metrics have some value in helping individual patients and families and advancing knowledge of the human body, while also leaving key gaps. The number of manuscripts published by the network—307 as of July 2, 2025—suggests the extent of UDN contributions to new knowledge about causes of rare diseases, particularly their genetic underpinnings.[3] Manuscripts published by the network also provide some additional insight into other relevant indicators of value, such as patients' experiences of participation,[6,7] parents' perceived utility of diagnosis,[8] and impact of diagnosis on

parent or patient empowerment.[9] However, these indicators are not systematically collected network-wide. The submission of 939 rare variants to ClinVar (a public database) and completed genome sequencing for 2078 participants as of July 2, 2025, have further contributed to the general knowledge base.[3] Metrics such as the number of new disease genes or new disease mechanisms identified by the UDN indicate that the UDN's contributions to science extend beyond those relevant just to participants in the UDN.

However, as with any scientific achievement, the true value of the knowledge gained is difficult to evaluate. Counting scientific manuscripts can provide insight into scientific productivity but does not speak to the quality of the information generated or its importance to individual patients or patient populations. Even if the journal in which a manuscript is published serves as a proxy for quality and importance, the true measure of the scientific value of health research could be thought of as the extent to which it ultimately changes clinical care and, ultimately, improves health outcomes. But even if the number of additional patients diagnosed outside the UDN increases as a result of this knowledge, the benefits of these diagnoses to the patients and families remain difficult to assess.

One way to understand the broader scientific value of the UDN could be through an examination of the value it provides to current participants. The number of diagnoses identified—886 as of April 1, 2025—certainly suggests the potential for direct benefit to patients and families.[3] Furthermore, studies conducted both in collaboration with the UDN and by other research groups have documented many challenges associated with living with an undiagnosed disease, including excess morbidity, off-target treatments, invalidation by health care practitioners, social isolation, and serious mental health consequence, among others.[10,11,12] Many of these challenges could be ameliorated by diagnosis.

However, the UDN does not systematically collect the data needed to assess whether the diagnoses it has provided have ameliorated any of these challenges. For one thing, it does not systematically collect information on health outcomes, and therefore it is unclear whether diagnoses have any impact on clinical outcomes for patients. Furthermore, while the network does collect limited information on the impact of diagnosis on parent or patient empowerment,[4] it does not systematically collect patient-reported outcomes related to personal utility or health-related quality of life—despite the fact that families can derive various forms of intrinsic or instrumental (eg, reproductive decision-making) value from a diagnosis and that most rare diseases lack treatments.[13] Beyond the post-evaluation surveys of participant satisfaction, it also is unclear whether the UDN is considering or actually measuring potential harms that might emerge from participation. Given the vulnerability of the participant population and its dependence on the research, there are risks of therapeutic—or diagnostic—misconception, which have been documented but are not currently systematically evaluated.[6,14]

How Should the UDN's Value Be Assessed?

Systematic evaluation of enrolled participants' health outcomes and impacts of diagnosis (if received) on participant and family quality of life would increase the scientific value of the UDN by providing unique insight into the clinical and personal benefits of diagnosis for a wide range of rare diseases, particularly those that are ultra rare and lack therapies. While research has suggested the potential for significant personal utility of a rare disease diagnosis,[8,15] this utility has not been systematically

assessed in a large sample of ultra-rare diseases. Such analyses could also provide insights into potential mediators and moderators of benefit to guide testing recommendations and follow-up outside of the UDN. In addition, studies have only rarely examined the perceived benefits of diagnosis over time,[16] and those that have done so suggest waning of perceived benefit.[17] Collecting patient-reported measures of value among UDN participants at multiple time points could help to fill this key knowledge gap. In addition, collecting and comparing diagnosed and undiagnosed patients' data on quality of life over time could provide insight into the extent to which diagnosis provides unique benefits to patients and families.

Maximizing the knowledge gained through the UDN is also consistent with the ethical practice of research. The risks participants take on through their participation, such as risks to privacy and financial risks of travel and time off work or school for assessment, are justified in part by the social value of the knowledge to be gained. Understanding the potential benefits and harms of participation from the perspectives of patients and families also is essential for ensuring true informed consent, as well as for understanding obligations to participants should UDN funding end. Current guidelines suggest that researchers have limited obligations to return results on genetic and genomic research to participants after studies end.[18] However, this obligation is arguably greater, as UDN participants are unique in having almost invariably exhausted all diagnostic testing available in clinical care. The obligation to return results even after the study ends is contingent, at least in part, on the extent to which sharing the information would provide direct benefits to the patient and family.[19] But without data on harms and benefits, we cannot effectively assess ethical obligations to participants enrolled in the UDN.

Clarifying how benefits and risks of UDN participation should be assessed is also central to determining the resources and infrastructure needed to maximize the UDN's value to enrolled participants and to science. The current structure of the UDN focuses scientific inquiry on the individualized evaluation of each participant. While this structure was a logical beginning for a small program, reenvisioning the UDN as a multi-site, longitudinal cohort study could further maximize both its scientific value and the value to participants. Collection of clinical and patient-reported outcomes over time, at regular intervals, using systematic and consistent protocols across sites rather than collecting outcomes data solely at the time of evaluation using variable protocols could help fully characterize the benefits of participation for patients and families and fill key gaps in our current understanding of the value of genetic diagnoses for highly heterogenous rare diseases over time. This approach could also provide clearer evidence as to the value of the UDN evaluation itself not only for science and for the patients who are diagnosed, but also for those who remain undiagnosed, some of whom have reported benefits simply from participation.[7,8] In addition, as tools for diagnostic evaluation evolve, a large cohort of rare and undiagnosed patients with well-characterized clinical, genomic, and patient-reported outcomes data could provide valuable data for evaluation of these new tools, further enhancing the value of the network to science. Finally, the UDN could follow the examples of other longitudinal cohort studies, such as the Framingham Heart Study or the Jackson Heart Study, in building lasting and collaborative, reciprocal relationships with participants and participant communities.

Conclusion

As a translational genomics study that seeks to both advance science and help patients and families, the UDN has the potential to provide unique insights regarding the value of

diagnosis. However, the current criteria used to assess the UDN's value in fact directly *limit* its value. Reenvisioning the UDN as a longitudinal cohort study that systematically collects clinical and patient-reported outcomes over time would ensure that the network can maximize its value to science, participants, and future patients.

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Dr Halley is a co-investigator for the Stanford Center for Undiagnosed Diseases, a clinical site of the Undiagnosed Diseases Network (UDN), and for the Data Management and Coordinating Center for the Rare Diseases Clinical Research Network. She is also the parent of a UDN participant and founder and board member emerita of the UDN Foundation. Dr Tabor disclosed no conflicts of interest relevant to the content.

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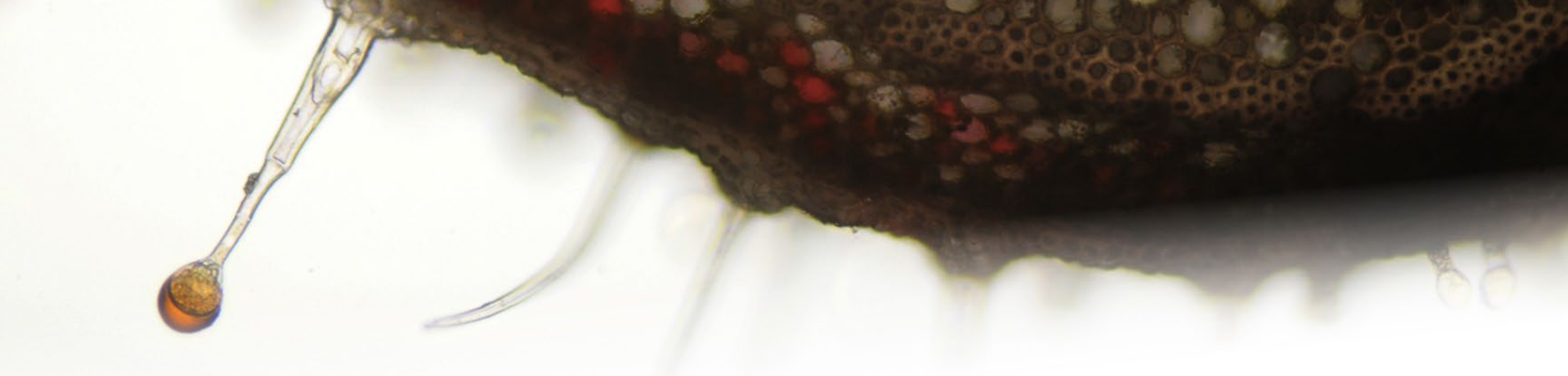

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HISTORY OF MEDICINE: PEER-REVIEWED ARTICLE

What Matters Ethically About How the UDN Has Changed Since Its Inception?

David A. Pearce, PhD and Elena-Alexandra Tataru, PharmD

Abstract

For persons living with an undiagnosed disease and their families, finding an accurate diagnosis can be a long and complex process. Having a rare condition that goes undiagnosed for a long period constitutes a significant part of these patients' disease burden. This article suggests the importance of international collaborative approaches to rare disease diagnostic practices and describes how the Undiagnosed Diseases Network can draw on best practices and clinical networks to motivate patient-participants' access to rare disease diagnoses.

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Role of Undiagnosed Disease Networks

Anyone with symptoms of a health condition expects to be diagnosed and has the hope of treatment for their symptoms. When it comes to unexplained and often unlinked symptoms and perhaps even complicated multi-symptomatic conditions, an accurate diagnosis, let alone a treatment, could be elusive. The Undiagnosed Diseases Network (UDN) strives to provide a diagnosis for individuals with unexplained health issues and for people living with an undiagnosed disease (PLWUD). UDNs, whether national or international, share common aims, including 3 priorities: (1) to accelerate diagnoses for PLWUD, (2) to "support and share knowledge and skills" to allow for development of more UDNs, and (3) to expand medical knowledge and promote discovery.[1] Consequently, UDNs remain international collaborations to help clinicians foster patients' access to a rare disease diagnosis. This article suggests the importance of international collaborative approaches to rare disease diagnostic practices and describes how the UDN can draw on best practices and clinical networks to motivate patient-participants' access to rare disease diagnoses.

Expanding Access to UDNs

With the growing expansion of UDNs worldwide (and particularly in the United States), patients now have the chance to possibly receive answers to their long-standing questions about the cause of their symptoms. Although UDNs are often country specific

and not coordinated at a national level, this situation is changing. In Europe, projects such as SOLVE-RD, launched in 2018 and funded by the European Commission for a period of 5 years,[2] have leveraged the experience of European Reference Networks for Rare and Complex Diseases best practices for data sharing within the European Union (EU), efficient partnerships between European medical centers, and reanalysis of data of patients who remained undiagnosed.[3] Moreover, tools such as the European Platform on Rare Disease Registration, developed by the European Commission's Joint Research Centre and Directorate-General for Health and Food Safety, have the role of making rare disease registries more visible across the EU and improving the fragmentation and standardization of patient data between registries.[4] In Asia, smaller-scale, country-specific programs such as BRIDGES (Bringing Research Innovations for the Diagnosis of GEnetic diseases in Singapore), established in 2014, aim at establishing collaborations between genomic research institutes, including at SingHealth (Singapore Health Services), the Agency for Science, Technology and Research, and Duke-NUS Medical School, for improvement of diagnosis pathways and patient outcome management, and these efforts have proved successful.[5]

Ethical Issues in Genome Sequencing

Access. In the last decade, advancements in genome sequencing have led to a shift from assigning a clinical diagnosis based on symptoms to finding a genetic diagnosis, as well as a clinical diagnosis.[6] However, barriers still exist to benefiting from and accessing genome sequencing. Clinicians might not be trained to interpret the results and, in some cases, even consultations with expert, specialized teams might not lead to a conclusive interpretation. Moreover, in many low- and middle-income countries, access to genome sequencing remains limited,[7] and patients coming from precarious environments or poorer countries are less likely to be studied or to be included in research pilots.[7,8,9] However, since the inception of UDNs, rapid advances and improvements in accuracy, interpretation, availability, and access to and cost of exome sequencing (ES) and whole genome sequencing (WGS) have occurred.[10,11]

Informed consent. Typically, PLWUD who enter a UDN program are considered research participants due to the fact that, in its raw sense, diagnosis is a "discovery"-based approach with no guaranteed outcome. In these cases, the role of the informed consent is fundamental in ensuring patients' understanding that there might be situations in which genetic variants are of unknown significance and thus a high probability of receiving inconclusive results, which might have psychological implications for patients.

Implementation. UDNs' role remains, predominantly, to review clinical information shared with PLWUD and to build a knowledge base of genetic information in public databases. Yet, despite significant advancements in clinical practices for undiagnosed diseases, no standard model exists at this moment for assessing PLWUD, which can lead to incomplete diagnostic profiles for some individuals. Worse still, as a second opinion might be needed, different interpretations of test results can occur, compounded by the absence of specific standards for genome sequence analysis. The learnings from genomic data are still, in many respects, at an incipient stage and open to human interpretation and prior experience. Thus, the following questions arise in terms of evaluating and communicating genetic information or results: What genetic testing should be done and what are its benefits?

What Tests Should Be Done and Why?

When dealing with an undiagnosed condition, clinicians order many tests, and which tests they order is often dependent on their previous experience. These tests are commonly explained to PLWUD, as with any test (eg, blood test) upon a doctor visit. At some point, PLWUD or their families might raise the option of a genetic test. Indeed, one of the biggest changes in rare disease diagnosis has been the growing number of patient requests for a "genetic" diagnosis. Several years ago, the method of genetic diagnosis would probably have taken the form of a panel that detects sequences of specific genes associated with specific types of conditions. For example, tests for metabolic and mitochondrial diseases or epilepsies are still currently in use. The particular panel ordered is frequently supported by the clinician's experience in the evaluation of symptoms and a suspected diagnosis of what might be a rare disease.

In UDNs, a diagnosis normally requires a more sophisticated method of assessment. Therefore, PLWUD might have additional results from ES or WGS to provide for a more comprehensive interpretation, although WGS is much more likely to be ordered to cast a broader net. Moreover, a less targeted approach, in a majority of cases, lends itself to sequencing the parents, commonly termed trios, of PLWUD, in the attempt to identify inherited mutations rather than de novo mutations. As a result, an overwhelming amount of information is gathered, much of which might not be relevant for a diagnosis. Even relevant information might not provide certainty. To be sure, a genetic diagnosis is likely to provide a named cause of the disease in terms of a gene name, or it might offer additional information on the medical condition and suggest a direction for seeking a clinical diagnosis. Ultimately, however, the genetic variant identified might be associated with and not the cause of the disease and thus might or might not provide closure for an individual.[12] Additional uncertainty is introduced if the evolution of a condition is, as in numerous cases, dependent on the onset age, gender, and general physical condition of PLWUD.

Regardless of the uncertainties that WGS might provoke, it offers several benefits. Making use of the available technologies in offering patients a "compromise" solution might help provide solace to PLWUD by giving them hope in potential solutions or alternative treatment approaches. Another benefit is growth of the knowledge base through adequate reporting of variants; the submission of variants to federated, regional, national, or international databases accessible to clinicians should become mandatory. To further build the knowledge base, a set of procedures should be established for periodic reanalysis of data and for identifying patients who present similar phenotypes or genetic mutations, and complementary use of other technologies should be considered (eg, methylation profiling, functional metabolomics studies) when sequencing alone is inconclusive for determining the underlying mutation.[13]

Conclusion

There is no doubt that UDNs have contributed to a significant increase in diagnoses for PLWUD due to the clinical use of ES and WGS.[14] However, WGS, regarded as the "gold standard" in terms of diagnosis technique, provides an interpretation of just 5% of the 3 billion base pair codes[15] and might ultimately leave many patients, who participate in UDNs with high expectations of a diagnosis, discouraged by the result (or absence of it). While not minimizing ethical issues that might arise during this process, it is important to remember that accessibility has always been a concern for any type of health care service. It would be interesting to assess the diagnostic success rates across the UDN and UDN International and to track diagnostic approaches in addition to genome

sequencing in different countries and cultures,[16] as well as to compare points of view about health care and support in relation to geographic region, economic development, health priorities, and regulations. Developing a set of standardized recommendations for communication of results based on new technologies, which takes into consideration the complex nature of diagnosis procedures, remains a long-standing goal in appropriately addressing the struggles of PLWUD.

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ART OF MEDICINE

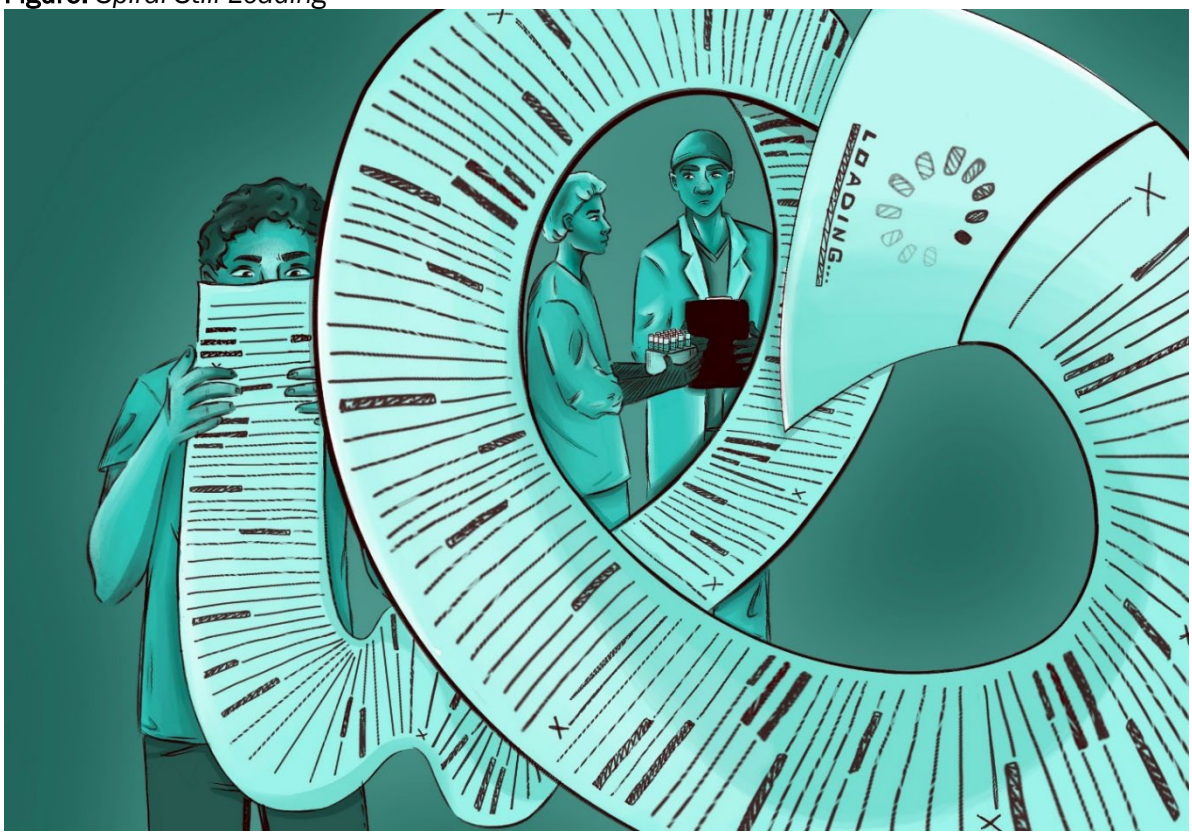
Decision-Making About Biospecimens

Anaid Kassidy Corona-Andaverde

Abstract

This digital drawing considers a signatory's experience of some consent processes in health decision-making that might involve their biospecimens' use in standard care, clinical research, or diagnostic research of the Undiagnosed Diseases Network.

Figure. *Spiral Still Loading*



Media

Digital illustration made with Wacom Cintiq, Krita, and iPad Procreate.

This digital drawing of a long, spiraling document suggests a confusing and lengthy consent process. Prospective risks and benefits of a clinical intervention can be too numerous to cover in a single clinical encounter, and risks of participating in clinical trials can be unknown. In both standard care and research settings, genomic and genetic biospecimen sampling adds to a list of social, psychological, and physical risks that can permanently alter the lives of participants and, at times, their biological relatives or descendants.[1] Psychological risks of participating in research, especially, can be "subtle and poorly defined" despite their importance.[1]

In 2019, the US Department of Health and Human Services revised the Common Rule to "provide key information and promote [the] autonomy" of subjects.[2] Revisions to informed consent regulations, in particular, also included an updated definition of the term *human subject* and updated informed consent exceptions.[2,3] Improvements in regulations or consent forms, "including simplified language, illustrations, shorter length, and teach-back approaches, have led to only modest improvements" in subjects' clearer understandings of research protocols and goals.[1] Consent processes that prioritize personal interactions between clinician-investigators and patient-subjects tend to hold more promise for promoting patient-subjects' understandings of their roles in research[4] and of how their biospecimens might be used.

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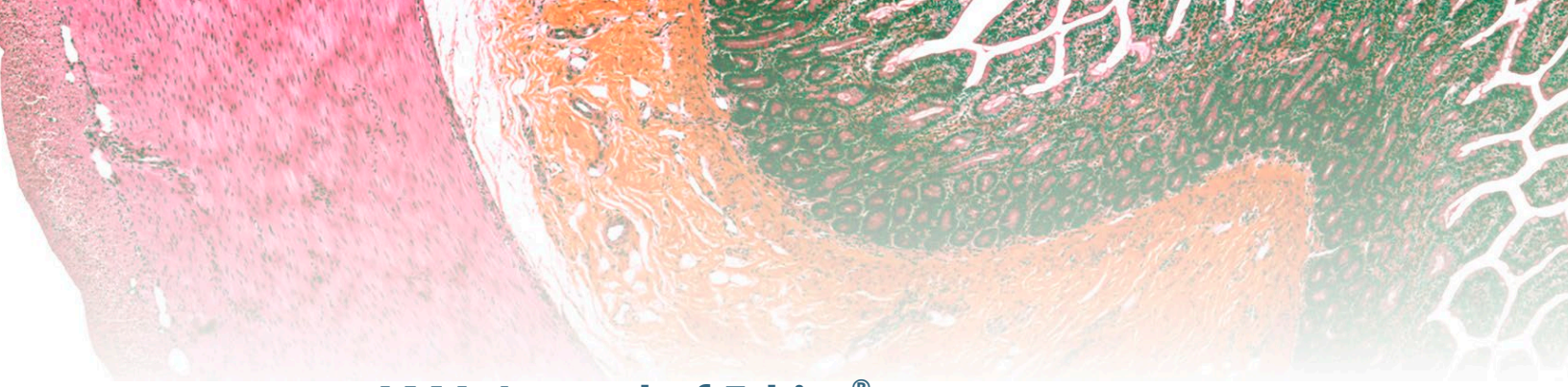

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LETTER TO THE EDITOR

Response to "How Should We Assess Quality of Health Care Services in Organizations Owned by Private Equity Firms?"

Joseph Dov Bruch, PhD, Sneha Kannan, MD, MS, and Zirui Song, MD, PhD

In "How Should We Assess Quality of Health Care Services in Organizations Owned by Private Equity Firms?," our colleagues Drs La Forgia and McDevitt expressed concern that flawed reasoning and cherry-picked findings on private equity (PE) in health care might misinform the public.[1] As researchers guided by scientific evidence and facts, we fully agree with this point in principle. Unfortunately, however, their article exemplifies the very practices they critique.

They argue that a paper by Kannan, Bruch, and Song[2] received unwarranted attention because hospital-acquired conditions "are exceedingly rare, making up 0.2% of all hospitalizations."[1] However, hospital-acquired conditions are a widely used quality measure and account for a greater proportion of total hospitalizations than other outcomes employed in work by McDevitt and colleagues (eg, in-hospital mortality for patients with acute myocardial infarction or 30-day mortality for patients with chronic obstructive pulmonary disease).[3] They also take issue that not all hospitals contributed data for the full 3 years before and after a PE acquisition,[2] but this is common in this area of research, including in work by McDevitt and colleagues.[4]

They further contend that, because the rate of falls and trauma remained constant in PE-acquired hospitals but declined in the control group,[2] it is inappropriate to interpret the difference-in-differences estimate as evidence of deteriorating quality. This argument selectively ignores the logic of all difference-in-differences approaches, including those they rely on in their own studies of PE,[4] and it misunderstands the role of the control group in causal inference. Advances in safety of hospital care reduced complication rates from 2010-2019 across US hospitals on average,[5] so the fact that care quality stagnated (ie, did not improve) in PE-acquired hospitals is, in itself, concerning.

La Forgia and McDevitt claim the article's key takeaway should be the observed decrease in in-hospital mortality, without acknowledging that relatively higher transfer rates and possibly earlier discharge of sicker patients among PE-acquired hospitals all point to the likely bias in patient selection by PE hospitals shown in the study—that PE hospitals admitted relatively younger and fewer dually eligible (particularly disadvantaged) patients after acquisition.

They conclude that PE is "good for fertility clinics."[1] Yet the very study they cite on fertility chain ownership—coauthored by La Forgia—clearly states, "PE funding does not influence the live birth rate," the main outcome evaluated.[6] The authors conclude: "This result suggests quality improvements occur because of the chain, not the PE funding," and PE funding instead drives an increased volume of in vitro fertilization cycles.[6] In fact, the increase in live births after PE acquisition is no larger (and indeed a bit smaller) than after acquisition by non-PE, for-profit chains.[6]

Given the authors' concern about media mischaracterization of research on PE, we are surprised to see their misrepresentation of their own findings and those of others in both this article and public commentary.[7,8] We respect colleagues who defend the role of PE in health care. In fact, we have consistently incorporated defenses of PE in our own lectures and public comments[9,10,11,12]—both to illustrate the nuances in this field and to accurately represent what the evidence shows and what the range of opinions about PE includes. However, defenses of PE on the grounds of objective evidence or informed opinion are different from defenses based on the mischaracterization of evidence or selective departure from scientific methodology. This is the distinction we draw in this response.

We are concerned about research that is funded by PE and believe that scientifically rigorous and non-ideological commentary might offer a more objective starting point for such discussion about the role of PE in health care, given the patient outcomes at stake.

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