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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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Editor's Note

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