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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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Tom A. Doyle, PhD is a postdoctoral fellow at the Indiana University Center for Bioethics in Indianapolis. Dr Doyle received his PhD in philosophy from Purdue University and completed a fellowship in clinical ethics at the Fairbanks Center for Medical Ethics at Indiana University Health. Dr Doyle's research interests are the phenomenology of medicine and patient experience with health care. He has published on a wide range of topics, ranging from patient education in pharmacogenomics to health care access for individuals with rare diseases.

Erin Conboy, MD is an associate professor in the Department of Medical and Molecular Genetics and Pediatrics at Indiana University School of Medicine in Indianapolis. Dr

Conboy received her medical degree from the Pennsylvania State University College of Medicine and completed her residencies at Mayo Clinic. Dr Conboy, with a multidisciplinary team, has established the Undiagnosed Rare Disease Clinic, which was recently awarded U01 clinical site status in the Undiagnosed Diseases Network.

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