VIEWPOINT

The Undiagnosed Diseases Network of the National Institutes of Health
A National Extension

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In 2008, an Undiagnosed Diseases Program (UDP)[1,2] was established within the Intramural Research Program of the National Institutes of Health (NIH). This program evaluates patients and families for whom medicine has failed to provide a diagnosis. Such patients have often spent years visiting medical centers and clinicians in different specialties across the country, accumulating large amounts of medical notes and test results, often at great emotional and financial cost. Indeed, patients who finally received a diagnosis through the UDP had spent 3 to 10 times more in physician consultation fees than consultations during their NIH evaluation (C. J. Tifft, written communication, 2015).

The absence of a medical diagnosis creates a measure of concern, and perhaps suspicion, on the part of a patient's family, friends, colleagues, and employer. Failure to establish a diagnosis can complicate and challenge the patient-physician relationship, which relies on the expectation that the cause of a disease can be identified and addressed. Yet for individuals with rare or novel disorders, the lack of a diagnosis occurs frequently. Of the 6000 annual calls to the Genetic and Rare Diseases Information Center, 6% are from persons without a diagnosis, and 15% of patients with rare diseases spend more than 5 years searching for a diagnosis.[3] Considering that the promise of tailored medical therapy depends so much on knowing the exact cause of a disorder, making a definitive diagnosis represents a huge unmet need.

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Participants in the UDP are chosen based on objective signs and symptoms, the unique nature of the problem, and an estimate by the UDP of its ability to make a diagnosis. From 2008 to 2015, only 25% of applicants to the UDP were accepted into the program, currently located at NIH; however, on September 16, 2015, a national extension to the UDP was launched. The NIH Undiagnosed Diseases Network (UDN), supported by the NIH Common Fund, consists of 7 clinical sites, 2 sequencing cores, a coordinating center, and soon, a central biorepository, a metabolomics core, and a model organisms screening center. By the summer of 2017, each clinical site is expected to see at least 50 patients per year, while the NIH site will continue to see 150 patients per year. The UDN launches with the opening of an online patient application portal, called the UDN Gateway, through which patients and their physicians can register and apply.[4]

Comprehensive clinical assessment represents only the beginning of the UDN's pursuit of a diagnosis. Patients typically spend a week as inpatients or outpatients undergoing extensive investigations including specialized laboratory studies, imaging, and most important, consultations from experts in rare diseases. A routine next step, in the age of next-generation sequencing, involves analysis of the exomes or genomes of the patient and family members, sometimes conducted before their clinical evaluation to inform the investigation. Another consists of functional studies of the effects of identified genes or variants, performed in patient cells or model organisms.

The approach has been successful. A 2-year report of the UDP[5] described the discovery of new diseases, new gene-disease associations, and diagnoses of truly rare disorders. Of 160 patients who were admitted to the service during the first 2 years, diagnoses were made in 39 patients. Diagnoses included 2 new undescribed disorders, 23 rare or ultra-rare diseases in 28 patients, and 9 common conditions, including psychogenic diagnoses, fibromyalgia, and multiple myeloma.[6] The UDP estimates that approximately half of its diagnoses were made directly from agnostic genetic testing such as exome sequence analysis. The remaining diagnoses were made by focused biochemical, radiologic, and molecular studies suggested by rare disease specialists given the opportunity to investigate the problem as a collaborative team. There has been no formal analysis of cost, and it is unknown if the clinical outcome for the patients who received diagnoses was improved.

Several innovations make the UDN more than merely an extension of the UDP. Each site expands the clinical expertise that is immediately available to patients across the network. The UDN has a single central institutional review board, located at the National Human Genome Research Institute. In addition, the patient consent form requests permission to share identifiable data with UDN members to aid in diagnosis as well as deidentified data with other investigators. Such sharing enhances the identification of

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other patients with similar presentations, a powerful tool of the global information age, fostered by social networks that readily connect individuals with shared interests. Indeed, families of patients with rare diseases increasingly seek these connections and network with others.

However, connecting diverse individuals with similar presentations does more than provide a social support network for the families. It augments the possibility of genetic discovery; if genetically unrelated individuals present with a similar set of signs and both have very rare genetic variants in the same gene, the probability that the gene causes the disease is increased. UDN investigations also include a comprehensive, standardized environmental evaluation as well as documentation of clinical signs via a standardized hierarchical classification system known as the Human Phenotype Ontology.[7]

When standardized methods for eliciting, documenting, and sharing clinical signs and environmental modifiers are combined with state-of-the-art genetic, biochemical, metabolomic, and immunological analyses, the chance of ending the diagnostic odyssey for families with undiagnosed diseases is maximized. Moreover, by delineating psychosocial and economic outcomes of the process, best practices are more readily achieved and maintained. In addition, an extensive and dynamic manual of operations describes these best practices so that other institutions can create similar programs.

The UDN brings with it many possibilities. It enables patients across the country to seek the services of the network, irrespective of their socioeconomic or geographic circumstances. It exemplifies data sharing allowing the patient to meet with the appropriate expert with all the relevant data, wherever that expert happens to be. It represents the practice of precision medicine,[8] with every laboratory test, consultation, image, and gene variant analysis geared toward the unique disorder of an individual. It provides the opportunity to identify confirmatory cases of new disease entities, allowing the assignment of causality to identified variants. It advances functional studies that will reveal new mechanisms of action, novel cellular pathways, and previously unrecognized drug targets. In addition, by fostering collaboration, the UDN is already beginning to serve as a model for the establishment of a worldwide consortium of undiagnosed diseases programs dedicated to discovery, diagnosis, and ultimately treatment.

The UDN is an ambitious new venture. Although leaders of the member institutions know they will succeed in some measure, despite best efforts, some patients will still not receive a diagnosis. Even then, there is value in moving families from stagnation to hope; the knowledge that a team of physicians and scientists will continue to work in the pursuit of a diagnosis can be very powerful. This reestablishes the bond with patients who live in diagnostic limbo, many of whom share the simple goal of helping others avoid the uncertain fate of the undiagnosed.

ARTICLE INFORMATION

Published Online: September 16, 2015. doi:10.1001/jama.2015.12249.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ashley reports holding stock in Personalis. No other disclosures were reported.

Funder/Sponsor: Research described in this article is supported in part by the Intramural Research Program of the National Human Genome Research Institute and by grants U01 HG007674, U01 HG007703, U01 HG007709, U01 HG007672, U01 HG007690, U01 HG007708, U01 HG007530, U01 HG007942, and U01 HG007943 from the National Institutes of Health Common Fund, through the Office of Strategic Coordination/Office of the NIH Director.

Role of the Funder/Sponsor: The funders had no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Additional Information: Members of the Undiagnosed Diseases Network include David Adams, Patrick Allard, Euan Ashley, Carlos Bacino, Alan Beggs, David Bernick, Jonathan Bernstein, Marishka Brown, Catherine Brownstein, Joy Cogan, Katrina Dipple, David Eckstein, Christine Eng, Paul Fisher, William Gahl, David Goldstein, David B. Goldstein, Tina Hambuch, Rizwan Hamid, Ingrid Holm, Howard Jacob, Issac Kohane, Brendan Lee, Joseph Loscalzo, Calum MacRae, Teri Manolio, Alexa McCray, John Mulvihill, Stan Nelson, John Newman, Christina Palmer, Mary Perry, John Phillips, Rachel Ramoni, Vandana Shashi, Edwin Silverman, Kimberly Splinter, Joan Stoler, Kim Strong, David Sweetser, Cynthia Tifft, Camilo Toro, Narayanan Veeraghavan, Eric Vilain, Matthew Wheeler, Anastasia Wise, Elizabeth Worthey.

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