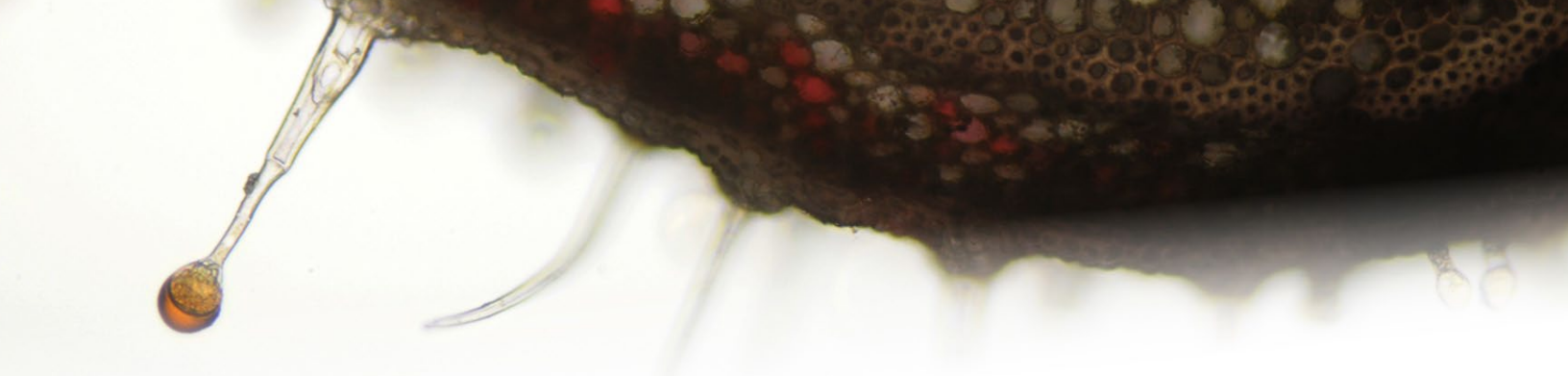

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What Matters Ethically About How the UDN Has Changed Since Its Inception?

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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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