A national program to diagnose difficult-to-diagnose patients

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Euan Ashley is the co-chair of the steering committee for a national program aimed at helping patients with difficult-to-diagnose diseases. Credit: Mark Tuschman

The National Institutes of Health's Undiagnosed Diseases Network launches today, and Euan Ashley, MRCP, DPhil, associate professor of cardiovascular medicine and of genetics at the Stanford University School of Medicine, has been named co-chair of the UDN steering committee.

The network, which seeks to provide answers for patients with mysterious conditions and to advance medical knowledge of both rare and common diseases, is an outgrowth of a smaller NIH program begun in 2008 called the Undiagnosed Disease Program. The new, expanded network inaugurates an online application gateway for patients, called

the UDN Gateway, that will harness the expertise of physicians at six major medical centers across the United States, while integrating patient access, patient consent forms and patient genome and other data through a single Internet portal. Within two years, the UDN expects to handle 250 patients per year.

Ashley, who co-directs Stanford's clinical genomics service and the Center for Inherited Cardiovascular Disease, is interested in precision health—the new approach to health that more precisely defines diseases to better understand them, predicts which individuals or populations are at risk and seeks to prevent disease.

After joining the School of Medicine faculty in 2006, Ashley developed a way to estimate a healthy patient's risk of disease based not only on traditional metrics, such as age, gender and family history, but by digging into the patient's genome. In 2013, Ashley was recognized by the White House Office of Science and Technology Policy for his contributions to personalized medicine. He is co-founder of Personalis Inc., a genetic diagnostics company.

In a recent interview with writer Jennie Dusheck, Ashley discussed the network's importance.

Q. You've written that the Undiagnosed Disease Network offers hope of ending the "diagnostic odyssey" of patients and their families. What is that odyssey like?

Ashley: We are used to devastating illness in medicine, but there's a particular torment that comes from having an undiagnosed illness. Of course, you have the symptoms and signs that any illness has, but just not knowing what it is—not having a name for it, not knowing what the

course of it is likely to be, not knowing if you share this with any other people—is a severe form of torment.

And I think in many situations, these individuals and families—because such diseases often afflict children—visit doctor after doctor and are increasingly frustrated. They are spending more and more of their personal time. It's a financial strain and an emotional strain, and they're telling the story again and again and again. If they have the resources, they'll go to one of the major academic centers. But in many cases, there are no answers—sometimes for years. And meanwhile, they are accumulating an expensive electronic trail of test results.

Q: How are patients selected to participate in the UDN?

Ashley: Generally, we'll focus on the families who are most likely to be helped. If there's clear evidence of a genetic condition, we have a greater chance of diagnosing that. If multiple systems of the body are involved in a very unusual way, or if test results are far out of the range of normal values, those are clues we can use.

For example, if someone's hormone level is four times normal, that gives us a clue. The challenge with genetic data—and we'll have a full genome sequence on every single one of these patients, which is remarkable in itself—is not so much finding the needle in the haystack as finding the right needle in a whole pile of needles. We all have genetic variations. The question is, which of them are important? But if we have blood tests or other results that point us clearly in one direction, that can help us decide which genes to look at.

One criterion we don't use is the ability to pay. Anyone may apply regardless of where they live or what their income is or whether they

have insurance, and they can be accepted into the network. Rare disease touches all sectors of society and certainly no one of us is immune.

Q: What are the main advantages of the new, networked UDN over the original, smaller NIH program? Where is this taking us?

Ashley: The original NIH program was designed to test this hypothesis: Is it possible to take the most concentrated group of experts and the full availability of diagnostic tests and apply that to these very difficult cases? Will the best that medical science has to offer do better than these often-futile diagnostic odysseys? The answer to that was a resounding yes.

Bringing together the experts and the latest technology doesn't take us to 100 percent. Only 25 to 35 percent of cases get some kind of solution, but that's far better than without the program.

The new, six-site network will increase capacity, so more patients can be evaluated. Secondly, not everyone can easily get to NIH, in Bethesda, Maryland. Adding five sites around the United States makes it easier for families to get to a clinic for expert evaluation. And we will also form a global network of such sites.

Another major effort has been to interconnect all the centers administratively, so they all operate as one. There's a single gateway where patients apply, and all the patients are distributed to the sites according to geography and site expertise.

If you have a common disease, you don't need to look very far for similar patients or doctors who know the disease. But with rare diseases, just adding one more patient can double the information you have. When

you find the second case of a rare disease, you really are in a new world in terms of understanding it. And with a network, the chances a patient will have access to an expert who has already seen the disease is much greater.

Q: What are the benefits of UDN—to patients, clinicians and researchers?

Ashley: The network does more than diagnose patients. Of course, just having an answer is a huge psychological benefit to families. But we're not going to stop there. The whole point is to find a way to treat it. And the way to treat it is first of all to understand the disease pathway.

The network also helps patients connect with one another and act as their own advocates. Parents and families can use the network and the Internet to find others with similar conditions. The medical literature is terrible for making such connections because it doesn't reflect the thousands of patients who are never diagnosed. But Google and social networks work beautifully to help patient families find one another.

Q: What proportion of patients with no diagnosis have a genetic disease versus some other kind of problem?

Ashley: Well, we don't know … ask me next year! Sometimes it's clear that the disease is genetic because four different family members all have the same disease. But if you have a kid with a new syndrome and the rest of the family is fine, it's much harder to tell if it's genetic or not.

In situations where there aren't clear family clues, we definitely look toward the non-genetic explanations. In fact, when Stanford applied to participate in the UDN, we featured our expertise in immunology and

infectious disease. Those are two of the major areas where we will work. Autoimmunity is a big frontier whose importance is only now becoming clear. And our ability to study the immune system is increasing dramatically.

We think of genomics as the tip of the spear for these new technologies and measurements. But just right behind that tip are high-throughput protein measurements and measures of immune system function, such as T cells and B cells. Our ability to use genomics to study infectious organisms is an exciting approach we hope to exploit at Stanford.

Looking at patients' environment is also going to be an important source of answers. Patients will fill out a comprehensive survey of standardized questions about their environment, but eventually we could make actual measurements of their environment.

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