Genetic Testing for EDS

I've resisted writing about the genetics of EDS until now, because it's a minefield of confusing information that I preferred to leave to the geneticists. However, increasingly the geneticists are refusing to see patients to diagnose EDS. So I feel obliged to explain why this is, and what to do about it – including how to get genetic testing without involving a geneticist at all.

Why genetics testing in EDS is usually unhelpful, and hard to get

If you're reading this you probably know that Ehlers Danlos Syndrome (EDS) is an inherited condition, and that some people get "genetic testing" for it. You're right, but there's more to it, as follows. EDS is a vaguely-defined group of conditions, with little more in common than a degree of looseness ("hypermobility") in a number of joints. About thirteen such conditions have been described and named, so far. We can expect further ones to be put up for inclusion in future. Most of these are very, very rare: some have only ever been described in one or two families. In most of these, affected patients are thought to have a single abnormal gene that governs the making of collagen. Collagen is a protein that is the main constituent of ligaments, tendons, and "connective tissue" in general. The prevailing theory is that the abnormal gene causes the collagen to be mechanically defective, so all the structures made of it are looser and more fragile than normal. (This theory is suspect, and may be seriously misleading. But this is not the place to go into that.)

Genes are "encoded" in the chemical, DNA. So genetic testing for EDS consists of analysing a patient's DNA to look specifically for the *known abnormal genes* that cause the body to make defective collagen. However, in one type of EDS, no abnormal collagen-gene can be found. And unfortunately, *this is by far the commonest type of EDS,* namely "hypermobile Ehlers Danlos Syndrome" or hEDS. This is also true of "hypermobility spectrum disorder (HSD)," a new category defined in 2017 by international agreement. This new label is quite confusing, in that there's no consensus on whether hEDS is actually part of the HSD spectrum, or something different from it. I'll refer to both together as "hEDS/HSD."

So if you have an Ehlers Danlos Syndrome, you probably have hEDS/HSD, which can't be confirmed by any genetic test. The diagnosis hinges entirely on the patient's medical history, family history, and findings on physical examination.

These conditions are now thought to be quite common: one person in every few hundred has one, which means that most high schools will have one or more students with an EDS-like condition. And awareness of EDS is increasing, hence the increasing number of people coming forward asking to be tested for it. But increasing numbers of geneticists are nowadays *refusing to see people for the diagnosis of hEDS/HSD*. Their waiting lists commonly go out over a year, and they simply can't handle the load of an increasing number of patients with a common condition for which they have no diagnostic tests. The trouble is that *treatment* of EDS is not done by geneticists but by various other specialists, each addressing one or two symptoms of a *multisystem* condition. And these specialists often don't want to acknowledge that a person has an Ehlers Danlos Syndrome unless it's been "officially" diagnosed by a geneticist.

Now, any doctor, nurse or physician assistant (PA) could actually diagnose hEDS and HSD, by applying a standard protocol for the history and examination. There's a very complicated one put out by the experts who redefined these conditions in 2017. It's displayed on the website of the Ehlers Danlos Society. It's dauntingly difficult to operate, so I've spelled out a simplified version on my website, called *Joint Hypermobility Diagnosis for Non-Specialists*. But almost no doctors want to use even this simplified version to diagnose hEDS/HSD. We are therefore in a stalemate position to which there's no obvious end in sight. As things stand now, the great majority of people with the commonest forms of EDS will not get a firm diagnosis from any of their doctors. So patients rightly ask, can they get tested for EDS without seeing a geneticist? First, I'll spell out what are the legitimate reasons for such testing, then explain how it can be obtained.

So why get tested for EDS?

There are three legitimate reasons for seeking genetic testing if you have, or think you may have, an Ehlers Danlos Syndrome. They are first, to rule out *vascular* EDS; second, to check if you have *another, very rare type of EDS*; and third, to search for conditions *other than EDS*, that can resemble it.

Vascular EDS (vEDS)

One of the rarer kinds of EDS is "vascular EDS" or vEDS. Like other rare kind of EDS, it can be strongly suspected based on the patient's history, family history, and physical exam findings. Unlike the common kinds of EDS (hEDS and HSD) there *is* a genetic test that can confirm vEDS. This is important, because vEDS poses a unique danger: blood vessels, and internal organs, can rupture spontaneously, leading to catastrophic internal bleeding that can be fatal.

People with vEDS generally have a personal history, and/or a family history, of these serious medical emergencies. But these emergencies also happen in many people *without* EDS. Examples are strokes caused by ruptured blood vessels in the brain, or ruptured aortic aneurysms due to splitting-open of the main artery in the chest and abdomen. And major bleeding in childbirth can have many causes, apart from vEDS. So a question comes up, when someone who looks to have an EDS knows of one or more of these events in their family, should they be tested for vEDS?

Unfortunately, there is no consensus on how to proceed in such a situation. But it's important to get this right, because the stakes are high. A woman with vEDS has a serious risk of dying of a stroke, or other catastrophe, at an early age; and there's a high risk for her children too. This will figure into her decisions about child-bearing. Also, if you have vEDS you should have certain scans done to see if you already have aneurysms that could be treated before they rupture. So doctors are likely to recommend testing for vEDS if any close relative has had a ruptured aneurysm or other organ, especially at an early age. Some would also run the vEDS test even if there were no such history, but the patient had physical features suggestive of vEDS. In both those categories, most of the tests turn out to be reassuringly negative, but one does not regret having done them.

Other, very rare types of EDS

Sometimes a patient has some features on examination, or in their family's health history, that point to one of the other, very rare types of EDS. These features are very variable. After examining the patient, the doctor may simply have the feeling that because of such findings, there may be "something else going on" other than hEDS/HSD, or vEDS.

Conditions that can mimic EDS
Various conditions can resemble EDS. The most well-known is Marfan Syndrome. Like EDS, it is inherited. Genetic testing helps identify it. However, this and other mimics of hEDS/HSD are much rarer than is hEDS/HSD itself. There is no test, or group of tests, currently available to screen for all of them. If your doctor wants to check for such conditions with genetic tests, they have to specify the conditions of interest and request a test for each one separately.

Ordering genetics tests yourself

Everyone knows that there are online companies that can do genetic tests without involving a doctor. The most well-known is *23andMe.* These tests mainly help in investigating *ancestry.* But their *medical* interpretations get a lot of criticism from geneticists. However, more than one legitimate *medical* genetic testing company has now opened its door to the public. As of February 2022, the main ones seem to be *Invitae*, and *GeneDx.* Both are relied on by medical geneticists and hospitals. They have good, user-friendly websites describing their services. Since these are evolving quite rapidly, I recommend getting a quote from each for the service you want, just as you might from two car insurance companies.

These companies can now run EDS tests on saliva, rather than blood. This means that you can get the tests done without any involvement of a doctor. The company sends you a package with a kit that enables you to take the specimen and mail it back to them. They can provide professional advice about which tests are appropriate for you, and explain what the results mean. Finally, the cost has come done several-fold in the last few years: from several thousand dollars, to a few hundred for most tests. The companies can help with insurance reimbursement. If you prefer to have your doctor handle ordering the test, then be aware that most doctors have never ordered genetic testing, so you'll need to tell them about these companies.

So, to sum up, if you have, or think you have, an Ehlers Danlos Syndrome, genetic testing usually won't help, because the great majority of people with an EDS have *hypermobile* EDS, or a Hypermobility Spectrum Disorder (HSD), and for these we have no confirmatory tests. However, if you're concerned you could have *vascular* EDS, or one of the other rare types, and you can't get a knowledgeable physician to assess your case, then Invitae or GeneDx can run the same tests that a geneticist would order, and will also interpret them for you, at a cost that is no longer in the thousands of dollars. But companies like *23andMe*, that mainly work with *ancestry*, are not recommended by geneticists for assessing EDS or most other inheritable conditions.

Alan Spanos MD
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Dr Spanos is in Chapel Hill, NC.
Other articles are on his website at *AlanSpanosMD.com*.