The
Ehlers
Danlos
Society™

INFORMED CONSENT DOCUMENT

TITLE OF STUDY: The Hypermobile Ehlers-Danlos Genetic Evaluation (HEDGE).

Sponsor: The Ehlers-Danlos Society

Primary Researchers: Clair A. Francomano, MD, Indiana University School of Medicine (cfrancom@iu.edu)

Woodrow Gandy, MD, The Ehlers-Danlos Society (woodrow.gandy@ehlers-danlos.com)

Source of Funding: Private grants to the Ehlers-Danlos Society.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS RESEARCH?

You are being asked to take part in this research study because you have (or may have) hypermobile Ehlers-Danlos syndrome (hEDS). Whether or not you take part in this study is up to you. If you choose not to participate, it will not affect your medical care.

This form explains the research study and your possible role in the study. Please read it carefully and ask questions before you decide. You may want to talk about this research study with your family, friends, and healthcare providers. Take your time. You should not sign this form until all your questions are answered. If you do decide to participate in the study, you must sign this form to show that you want to participate.

WHAT IS REQUIRED TO PARTICIPATE IN THIS STUDY?

To become part of this study, you must:

- Be between 16 and 99 years old; and
- Meet the criteria for hypermobile Ehlers-Danlos syndrome (from the 2017 diagnostic criteria); and
- Have created an account in the Ehlers-Danlos Syndrome and Related Disorders Registry; and
- Have completed surveys in the Ehlers-Danlos Syndrome and Related Disorders Registry; and
- Have set your preferences to allow researchers to view and use your data; and
- Be willing to have your blood drawn at your home or other preferred location.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study will enroll up to 1,025 participants, including men, women, and children.

WHY IS THIS RESEARCH STUDY BEING DONE?

This research is needed to discover the genetic cause of hEDS. We will do this by examining (sequencing) your genes and other parts of your DNA that may be associated with hEDS. We are also

looking for clinical markers or trends that may allow us to better understand hEDS or provide a diagnostic test

HOW LONG WILL YOU BE IN THIS STUDY?

Enrolling in this study should take approximately 1-2 hours plus any travel time related to the blood sample collection. You will not have to do anything further, however, we may study collected DNA indefinitely.

PARTICIPATION IN THIS STUDY IS VOLUNTARY

Your participation in this study is voluntary, which means you may choose not to take part. Your decision will not affect any relationship with your doctor or healthcare provider, and it will not result in any loss of benefits.

CAN I DECIDE TO WITHDRAW FROM THIS STUDY?

You may withdraw from the study at any point. If you withdraw before your DNA is sequenced, we will not include your DNA. If you withdraw after your DNA is already sequenced, we will permanently delete the information that allows anyone to connect your DNA information to you. However, we will not destroy the DNA sequence data itself and will continue to include it, along with other information, in the data being analyzed. Since the information connecting your DNA to you will be destroyed, we will not be able to report any results to you.

WHAT WILL YOU DO IN THIS STUDY?

If you choose to participate in this study, we will first determine whether you meet the 2017 criteria for hypermobile Ehlers-Danlos syndrome. If you do not meet those criteria, you will not continue in this study. However, if you meet the criteria for hypermobile spectrum disorder (HSD), you may be able to participate in a later HSD study. We plan to continue this work by studying HSD.

If you continue in the study, we will draw blood to determine your DNA sequence and to look for other findings that may help us understand hEDS or develop diagnostic tests.

HOW DOES DNA INFORMATION WORK?

Our DNA contains the instructions for how our body works. DNA is a complex chemical substance that includes our genetic information. DNA is how parents pass on their genes to their children. DNA is a molecule found in nearly every cell of your body and is visible only with a special microscope. The bases or “letters” of the DNA make up the “sequence.” Whole genome sequencing can reveal the entire code, including all the genes as well as all the other regions of the DNA. Alterations in these genes or these other regions of DNA can play a major role in the onset of a wide variety of human diseases.

HOW WILL THIS STUDY ANALYZE DNA?

A lab will analyze study participant DNA for research purposes. The lab will then report all of the genetic information to Ehlers-Danlos Society researchers who will be looking at the DNA sequence of all of the people in the study. We hope this will uncover which genes cause hypermobile Ehlers-Danlos syndrome (hEDS). By signing this form, you are agreeing to have your DNA sequenced, and allowing the research team to receive and analyze the results of your DNA sequence.

REPORTING OF RESULTS

If we publish an article about the study, we will notify you. We will not identify you individually in any article we publish. We will keep you posted on our progress by sending e-mail messages through the registry. In addition to this, you may "opt in" to receiving results from this study that fall into any or all of the following three categories.

Genes involved in hypermobile Ehlers Danlos Syndrome. If we discover one or more variations in genes that we believe cause or contribute to hEDS, you may receive that information. If you opt in, we will notify you by e-mail if you have that genetic mutation. If possible, we will try to provide detailed information. You can then share the information with your doctor or anyone else. We could make such discoveries within 2 years, but it also could take longer. It is difficult to predict.

☐ Please inform me about genetic variants you discover related to hypermobile Ehlers Danlos Syndrome.

☐ No, I do not want to receive this information.

Genes already known to cause a form of EDS. We may discover that you have a mutation already known to cause a form of EDS. You may receive that information if you opt in. In this case, we will contact you only if we do find such a mutation. We will arrange one free session with a genetic counselor. Depending on your location, the counseling session may be done on the Internet. We will not communicate directly with your doctor, but you may provide the results to your doctor. This information should be available within a year of beginning the DNA sequencing.

☐ Please inform me if you discover that I have a mutation in a gene already known to cause a form of EDS.

☐ No, I do not want to receive this information.

Other genetic findings we think you should know about. In performing our research work, we may notice a mutation in one or more other genes unrelated to EDS that we believe you should know about because of actions you could take. You may choose to receive this information or not. If you wish to receive information about significant mutations unrelated to EDS, please indicate this below. We will contact you only if we do notice such a mutation. We will arrange one free session with a genetic counselor. Depending on your location, the counseling session may be done on the Internet. We will not communicate directly with your doctor, but you may provide the results to your doctor or genetic counselor. We expect such information would become apparent within a year of beginning the DNA sequencing.

☐ Please inform me if you discover such other findings you believe I should know about.

☐ No, I do not want to receive information about incidental mutations that may pose a risk to my health or to my life, for which there are actions I could take.

IMPORTANT NOTICE: OUR RESEARCH GROUP IS NOT A MEDICAL TESTING LAB, SO YOU SHOULD NOT SUBSTITUTE PARTICIPATION IN THIS STUDY FOR OBTAINING RECOMMENDED MEDICAL LAB WORK. YOU SHOULD NOT RELY ON THIS STUDY TO RULE OUT ANY IMPORTANT FINDINGS.

CONSENT TO SHARE INFORMATION WITH GENETIC COUNSELOR

☐ I understand that I could have a genetic mutation that causes a type of EDS. I also understand that my genes could have a mutation that could be important to know about because of actions I could take. I understand that if the researchers discover such mutations in my genes, they will refer me to a genetic counselor. I agree that the research team can share this information with the genetic counselor.

☐ No, I do not want my information shared with a genetic counselor.

ARE THERE ANY RISKS OR PROBLEMS FROM THE GENOME STUDY?

Blood collection risks. Some people become faint with blood draws. The phlebotomist knows to watch for that and will help you if that happens. There is a very small chance of infection or inflammation at the blood draw site.

Risks associated with genetic testing. There is a chance that you could have psychological stress from participating in this study. Some people involved in genetic studies have felt anxious about the possibility of carrying an altered gene. If these feelings arise at any time during the study, we recommend that you speak with a genetic counselor. If you would like a referral to a genetic counselor, please contact Izabelle Manning at research@ehlers-danlos.com.

Gathering genetic information could cause social or economic disadvantages. We might find a defective gene that puts you at risk for a genetic disorder. Sharing genetic information with the wrong individuals could affect you and your family. For example, this could happen if an insurance company or employer acquired this information. However, we will not give any results with your name to anyone without your permission. We will not place the results in your medical record. We will not share the results with any insurance companies or employers.

There are also two laws you should know about. One is the Genetic Information Non-Discrimination Act (GINA). The other is the Health Insurance Portability and Accountability Act (HIPAA). These laws provide important protections by saying that health insurers and plan administrators may not generally request or require genetic information. They also may not use any genetic information for decisions regarding coverage. They may not use genetic information to set rates. They also may not use it to determine preexisting conditions. Most employers may not use genetic information for hiring, firing, or promotion. There are limitations to GINA's protections, however. They do not extend to life insurance, disability insurance or long-term care insurance. HIPAA requires your medical records be stored securely and prohibits release of your medical records without your permission.

WILL YOU BENEFIT FROM BEING IN THIS STUDY?

There is probably not going to be direct benefit for you or your family by participating in this research. However, we hope the study will help doctors understand the causes of hypermobile Ehlers-Danlos syndrome. It may lead to the discovery of other forms of Ehlers-Danlos syndrome. It may also eventually help researchers find new ways to diagnose the condition earlier and/or find new treatments.

You should not assume that your participation will rule in or rule out any medical problems for you personally. There are no doctor-patient interactions in study participation. The research may be shared with our collaborators and may lead to commercial products. Volunteering to be a donor of biological specimens and information does not give you any right, title, or interest in the specimen. It also does not give you any right, title, or interest in any derivative materials or products from this research.

WHAT OPTIONS OTHER THAN THIS STUDY ARE AVAILABLE TO YOU?

This is not a treatment study. Your alternative is to not take part.

WHAT HAPPENS IF YOU ARE INJURED AS A RESULT OF TAKING PART IN THIS STUDY?

There is a very low risk of injury from this study. The Ehlers-Danlos Society cannot offer financial compensation if you are injured because of this study. The Society also cannot pay for medical treatment should you be injured in this study. Your medical expenses will be your responsibility or that of your insurance provider. However, if those involved in this research are at fault for your injury, you may seek to collect compensation from them.

HOW WILL YOUR DATA AND PRIVACY BE PROTECTED?

The Ehlers-Danlos Society will protect your medical records and other personal information to the extent allowed by law. We will take the following measures to protect your data.

Blood sample and DNA sequencing. If you enroll in this study, a reputable laboratory will sequence your DNA. Our analytic team will receive your sequence data, labeled only with a coded identifier. We will store your genome data in a separate system from your identifying data, so it will be safer and difficult for an unauthorized person to obtain genetic information and know who it belongs to. They would have to breach two different systems to do that. Only the EDS Society will have the "key" connecting you to your genome data. This key will be destroyed after the study is complete.

Genome Sequencing Results. The EDS Society will inform you of genetic results through the society's EDS Registry, a web conference, or an in-person meeting. All these are secure and private methods. Please see "Reporting of Results."

We would like your permission to enter any genetic results in your registry account. If you allow this, it will make your registry information more complete. This information is subject to the same protections as the other data you provide in the registry. Having this information in the registry will allow researchers to find people for future research. If you choose not to have us add it, you can always do so yourself. If someone breaches the registry's privacy somehow, they could obtain this information.

Please select and initial one of the following options:

☐ **Yes, you may enter my genetic results into my registry account. I understand this data will be available according to my privacy settings. Depending on my settings, the information available to a given entity may include my identifying information.**

☐ **No, please do not enter any genetic results into my registry account.**

Other Study Documents. The Society's research coordinator will keep a copy of this consent form and other paper documents in a secure environment. This consent will not go into your medical record. Likewise, none of the information collected during the study or the results of the tests will go in your medical record unless you place it there with your medical provider.

We may share your sample and/or research data with outside researchers who have an interest in the genetic cause(s) of Ehlers-Danlos syndrome. In this case, we would release your sample and/or research data without your name or other identifying information.

Only those individuals named in this consent will have access to your information. Your name will not be revealed in any reports or publications resulting from this study without your permission.

FUTURE USE OF SAMPLES

We will store your DNA and information indefinitely for future research. However, when we complete our research, we will permanently delete all information that could link your DNA or genome information back to you. Researchers approved by the Principal Investigators of this study can request this data and samples for new research. We may share these de-identified samples and data with outside investigators as well as commercial entities. We will not ask you to provide additional informed consent for the use of your de-identified information or samples. Future research studies may include genetic research. There is a risk that someone could re-link your genetic information to you if they compared your genetic information to that of your other family members. We will require that any recipients of this information promise not to do this and will not release the information if we believe that is their intent.

PERMISSION TO CONTACT YOU IN THE FUTURE

We would like permission to contact you in the future in case we would like to obtain more information. If you do not want to be contacted in the future, please check the box below and write your initials next to it. Your participation in any future research study is completely voluntary. You should feel no pressure to participate if you are contacted about another research study.

☐ **Yes,** I want to be contacted in the future about further EDS research studies.

☐ **No,** I do not want to be contacted in the future about further EDS research studies.

INVESTIGATOR STATEMENT

The Ehlers Danlos Society may pay a fee to participating investigators to cover their costs and efforts. If you have any questions about our relationship and your physician, you may contact Izabelle Manning at research@ehlers-danlos.com.

WHO DO YOU CONTACT IF YOU HAVE STUDY QUESTIONS OR CONCERNS?

If you need more information concerning the research, please contact Izabelle Manning at research@ehlers-danlos.com or at 1 (410) 670 7577. You may contact the Genetic Alliance Institutional Review Board if you have questions about your rights as a research participant or if you have an adverse event related to this study at irb@geneticalliance.org.

TYPE OF CONSENT PROCESS

Please check and initial one:

☐ I met **in person** with a HEDGE representative.

☐ I had a **private teleconference** with a HEDGE representative.

☐ I did not have an in-person meeting or private teleconference, but I viewed a **presentation** or participated in a **group teleconference.** I was offered a private individual teleconference, but I had all my questions answered and do not wish to have a private one-on-one session.

GDPR Data Privacy Addendum (for European Union)

As a citizen or resident of the European Union, you are protected by the EU's General Data Protection Regulation (GDPR). This informed consent form provides much information required by GDPR, such as the sponsor of this clinical trial (the Ehlers-Danlos Society) which will control the data. It explains that the trial will utilize medical and demographic information you provided in the Ehlers-Danlos and Related Syndromes Registry and during the screening process, as well as your blood sample for genome sequencing.

You have these rights under GDPR:

- The right to request information about the handling of your data.
- The right to request correction of data if it is inaccurate or incomplete, and to restrict processing of that data while it is being corrected.
- The right to request transfer of the data we have collected to you or to others in a commonly used format.
    - For scientific integrity, access to some of the data may not be allowed until the study ends.
- The right to withdraw consent at any time, including the right to withdraw from study participation, follow-up or handling of further data, except for data already processed.
- The right to request deletion of your data if the data are no longer needed, or there is no other legal requirement for their use. However, there is an exception to this right for scientific research such as this project.
- The right to file a complaint with a data protection authority.
- The right to know the recipients or categories of recipients of your personal data, if any, and the identity of the people who may have access to the data.

Your blood sample will be transferred to a repository in the United States, where it will be protected consistent with the protections afforded through the GDPR. Your genome sequence, once determined, will be maintained in a secure environment and will not be labelled with any personally identifying information. Only the Ehlers-Danlos Society will have access to the key that can link your genomic information with your identifying information. This information will be stored in a separate computer system from that where your genomic information is stored and will be protected by passwords and firewall. Additionally, this information will be encrypted. Once this study is completed, the files linking your identifying information to the genomic information will be deleted and destroyed, but we will maintain the genomic information indefinitely, as described in the consent form.

The clinical information we obtain during screening at a site within the EU will be entered into Genetic Alliance's PEER registry system and will be available to authorized users of that system both within and outside the EU. You control who has access to that information through the permissions you grant within PEER. Since your genome will not be sequenced in the EU, no genomic data will be transferred from the EU to recipients outside the EU. If there is a need to transfer your genomic data from the secure environment at the company performing the sequencing to researchers, it will be transferred as encrypted de-identified files (i.e., without information linking it to you). The genomic data will then be stored as de-identified, encrypted files in a protected network environment. Your data will be stored indefinitely, but the separate file linking your genome sequence to your identifying information will be destroyed upon completion of this study. Your genome will not be placed into the PEER registry system, but information about certain mutations or variants may be entered if you have granted permission and consented specifically in writing for this to be done.
The European Union has not confirmed that the United States has mandated an adequate data protection level. The measures we will take in protecting your data goes beyond that mandated by law in the United States.

The Ehlers-Danlos Society Biobank

The Ehlers-Danlos Society is a member of the Genetic Alliance Biobank that provides storage facilities and support for organizations like the Ehlers-Danlos Society to collect biological samples and clinical information to help further research. By signing this consent, you are allowing us to include your sample in the Ehlers-Danlos Society Biobank located at the Genetic Alliance Biobank. This bank is funded by the Ehlers-Danlos Society. Please note that the Genetic Alliance BioBank does not see your contact information, nor make any decisions about your samples. It is used to provide the Ehlers-Danlos Society with cost effective storage space. It is up to you to decide if you want to give a biological sample to the bank by participating in this study.

If you decide you would like us to destroy your samples in the Biobank, we will do so if possible. This may not be possible if our research has concluded and we have removed the information that connects you to the sample, as we would not know which sample is yours. It is important to know if there is any possibility that another sample of yours already exists in the Genetic Alliance Biobank. If you have donated a sample in the past to a researcher, please let Izabelle Manning know via research@ehlers-danlos.com or 410-726-5329.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health as it relates to the Ehlers-Danlos Society Biobank. The researchers with this Certificate are not allowed to share or use information, documents, or samples that can identify you in any federal, state, or local case or be used as evidence, unless you tell them they can. Information, documents, or samples protected by this Certificate cannot be shared with anyone who is not connected with the research unless there is a law that requires sharing (like to report child abuse), if you said you would like to share, or if it is used for other studies that have been approved.

STATEMENT OF VOLUNTARY CONSENT

I have read this form or have had it read to me. I have been told what to expect if l take part in this study, including possible risks and possible benefits. I have had a chance to ask questions and have had them answered to my satisfaction. I have been told that the people listed in this form will answer any questions that I have in the future. If I am in the European Union, I have also read the GDPR Privacy Addendum. By signing below, I am volunteering to be in this research study. I designate the Ehlers-Danlos society as my representative to receive the results of the sequencing of my DNA.

Participant's Name (Print): _____

Phone number(s):_____ E-mail:_____

Signature: _____ Date: _____

A SIGNATURE IS REQUIRED IN THIS SECTION IF THE PARTICIPANT IS A MINOR OR OTHERWISE NOT LEGALLY ABLE TO CONSENT.

Legal Representative's Name (Print): _____

Relationship to Participant (e.g., Parent, Spouse, Legal Guardian) (Print): _____

Signature: _____ Date: _____

Legal Representative's Name (Print): _____

Relationship to Participant (e.g., Parent, Spouse, Legal Guardian) (Print): _____

Signature: _____ Date: _____

A WITNESS SIGATURE IS REQUIRED IF THE PARTICIPANT CANNOT READ OR SIGN THE FORM THEMSELVES (for example, due to a medical condition or language barrier).

The witness must be impartial and cannot be a member of the research team.

I verify that the participant was provided with and understood the information in the consent form.

Witness's Name (Print): _____

Signature:_____ Date: _____

Witness to: ☐ Discussion ☐ Signature

STUDY REPRESENTATIVE SIGNATURE

Study Representative's Name (Print): _____

Signature: _____ Date: _____

You will receive a copy of this form after it has been signed and dated by the Study Representative.