NCGENES: North Carolina Clinical Genomic Evaluation by Next-generation Exome Sequencing

Making Decisions About Learning Non-Medically Actionable Incidental Genetic Information From Whole Exome Sequencing (WES)

NCGENES is a research project at UNC-Chapel Hill.

We are studying a new kind of genetic test called “Whole Exome Sequencing” or WES to find out:

How good is WES at finding genetic causes of health problems?

How do people understand and react to the results they learn?

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About This Brochure

This brochure provides information to help you make a decision about whether or not to learn certain kinds of information that might be found from your Whole Exome Sequencing (WES). In NCGENES, we call this type of information “non-medically actionable incidental information.”

We encourage you to read this brochure before coming to your study visit so we can discuss it in more detail. There are spaces in this brochure for you to write down your questions or concerns as you think of them. You will not be asked to make your decision about whether or not to learn any of this information during the visit.

The brochure begins by describing Whole Exome Sequencing. It then describes the six types of non-medically actionable incidental information that you might decide to learn in NCGENES. This kind of information can be related to some health problems, but learning this information does not allow you and your doctor to take specific steps to prevent symptoms from happening.

After you return home from your study visit, you may wish to discuss this information with your family to help you make a decision. If you decide to request any of this information, you will then need to call the NCGENES study office to schedule either a telephone consultation or one or more additional study visits depending on which information you decide to learn. The chart on page 5 summarizes the different types and how you can request them.

Some types of non-medically actionable incidental information can be placed into your UNC Hospitals’ electronic medical record (EMR). You will be asked to decide which, if any, you wish to have placed there. Once a result is placed into the medical record, it cannot be removed.

The success of this research study does not depend on which decisions you make. We are most interested in finding out what information people choose to learn. After carefully considering your options, you should make the decisions that are best for you and your family.
About Whole Exome Sequencing (WES)

WES Can Find Some Genetic Causes of Health Problems

WES can find genetic causes of some health problems. Genes are the instructions used by our cells to make different proteins in our body. Proteins, along with our environment, affect how our bodies are made and how they work. All genes have the same four DNA bases: “A”, “C”, “T”, and “G”. The order of the DNA bases in a gene is called the “sequence.”

DNA sequences tell the cells in your body which proteins to make and how to make them.

For example:

DNA sequence ->>->->->->->->->-protein ->>->->-body structure and function

Gene 1 ...ACTGACTGACTGG...->>->->-=> protein “A” ->>->-> digests milk
Gene 2 ...AGGATCGATCC...->>->->-=> protein “B” ->>->-> affects heart rate

WES Finds Many Gene Variants

The DNA sequence of a single gene is not exactly the same in everyone.

For example:

Most people have this version of Gene 1: A C C G C T A T G C G C T A...

A few people have this version of Gene 1: A C G G C T A T G C G C T A...

These differences in genes are called “variants.” WES reads the sequences of the DNA bases of many genes at the same time and finds many thousands of variants. As in the example above, most variants have no known effect on health.
The Information Found from WES Is Limited.

There are many limitations to WES. Some variants that are found may give you some information about your health but most variants will not tell you anything about your health. Most often we don’t know and can’t predict whether or not a variant will have an effect on health. And, WES will not find all the variants that could possibly affect your health.

WES Can Provide Diagnostic Information

The main reason that you had WES was to see if it could find genetic variants that explain the health problem or the diagnosis that led you to join NCGENES. When WES finds genetic variants that caused this health problem, we call it a “positive diagnostic result.”

In the previous example:

Most people have this version of Gene 1: A C C G C T A T G G C C T A…
A few people have this version of Gene 1: A C G G C T G T G G C G C T A…

This variant has no known effect on health

Example of a positive diagnostic result:

People who have a specific health problem have this version of Gene 1: A C C G C T A T G G C C T A…

This variant explains the person’s health problem

In addition, WES can find many other variants in other genes that are not related to your diagnosis but that may affect your health in other ways. That is because WES finds the DNA sequences of many genes at the same time. Most gene variants are not related to your diagnosis. The information provided by unrelated variants is called “incidental information.”
In Very Rare Cases, Incidental Information Will Be “Medically Actionable”

Rarely, WES may find a genetic variant that 1) is unrelated to your diagnosis (incidental) and 2) causes a serious disease that can be prevented (medically actionable).

We call the information learned from these kinds of genetic variants “medically actionable” because there are definite actions that you and your doctor can take to use the information to help prevent disease.

In NCGENES, we will look for rare variants in the small group of genes that provide medically actionable information. If your WES finds a variant in this group, and if it is confirmed in the UNC Hospitals’ Molecular Genetics Laboratory, you will be told this medically actionable incidental information because knowing it could very important to your health.

Most Incidental Information Is NOT “Medically Actionable”

WES may find other variants that provide information about health problems that are unrelated to your diagnosis (incidental), but learning that you have this type of variant does not allow you and your doctor to take specific steps to prevent these diseases (not medically actionable).

We call the information learned from these variants “non-medically actionable” because there are no definite actions that you and your doctor can take to use it to help prevent disease.

Making Decisions about Learning Non-Medically Actionable Incidental Information

You will be asked to decide whether or not you want to learn any types of non-medically actionable incidental information that may be available from your WES. Different people make different decisions about whether or not to learn any of this kind of information.

In NCGENES, there are six different types (A-F) of non-medically actionable incidental information that you might decide to learn. Each of these types is briefly described below.

Types of Non-Medically Actionable Incidental Information in NCGENES

Type A: variants, called SNPs, that may slightly affect your risks for common diseases;

Type B: variants that affect how your body responds to some medicines;

Type C: variants that do not usually affect your health but that increase the risk for health problems in your children and others in future generations;
Type D: variants in the *APOE* gene that affect your risk, as compared to the average person, of getting the common form of Alzheimer’s Disease (AD);

Type E: rare variants in genes that directly cause you to have an increased risk for a genetic disease that cannot be prevented, but that may have some treatments after symptoms develop.

Type F: very rare variants in genes that directly cause severe and progressive diseases of the brain and nervous system that cannot be prevented and that have no effective treatment after symptoms develop.

Each of these types (A through F) is described in more detail in this brochure.

This chart explains some of the differences between these six types of information.

<table>
<thead>
<tr>
<th>Type</th>
<th>Description of Risk</th>
<th>Examples</th>
<th>The Result You Are Most Likely to Learn</th>
<th>Medical Management</th>
<th>How to Learn Results</th>
</tr>
</thead>
</table>

**NCGENES: Non-Medically Actionable Incidental Information**
<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Common Diseases</td>
<td>Typical forms of heart disease, cancer, and diabetes</td>
<td>Average or slightly different risk compared to the general population</td>
<td>Routine recommendations such as eating right and getting exercise.</td>
<td>Telephone</td>
</tr>
<tr>
<td>B</td>
<td>Differences in Response to Some Medications</td>
<td>Response to the blood thinner, Coumadin</td>
<td>Average or slightly different risk compared to the general population.</td>
<td>Possible change in the amount of medicine or avoidance of other medicine</td>
<td>Telephone</td>
</tr>
<tr>
<td>C</td>
<td>Carrier Status</td>
<td>Cystic fibrosis, sickle cell anemia, many others</td>
<td>Everyone is expected to have 4-8 positive results.</td>
<td>No personal health problems</td>
<td>One in-person visit</td>
</tr>
<tr>
<td>D</td>
<td>Common Form of Alzheimer’s Disease</td>
<td>Typical form of Alzheimer’s Disease</td>
<td>Average or slightly different risk compared to the general population</td>
<td>Routine recommendations such as eating right and getting exercise.</td>
<td>One in-person visit</td>
</tr>
<tr>
<td>E</td>
<td>Rare Genetic Diseases</td>
<td>Adult polycystic kidney disease, factor V Leiden; many others</td>
<td>Normal</td>
<td>For some conditions, some symptoms can be treated</td>
<td>One in-person visit</td>
</tr>
<tr>
<td>F</td>
<td>Rare, Severe, Progressive Diseases of the Brain and Nervous System</td>
<td>Lou Gehrig’s Disease (ALS); others</td>
<td>Normal</td>
<td>No prevention No treatment</td>
<td>Two in-person visits</td>
</tr>
</tbody>
</table>

Additional differences between the types of information are described in this brochure including:

- Some types of information can be learned by phone while other types are learned during a study visit.
- Only some types of variants will be confirmed in the UNC Hospitals’ Molecular Genetics Laboratory.
- You will be asked to decide whether or not to have the confirmed variants placed into your UNC Hospitals’ Electronic Medical Record.

The Effect of Learning Non-Medically Actionable Incidental Information

We do yet not know if learning this information will help, hurt, or have little effect on you.

Learning non-medically actionable incidental information:

- except for type F, does not tell you whether or not you will develop the disease.
• does not lead to specific steps for you and your doctor to take to prevent symptoms.
• might affect how you make other decisions about your life.
• might be helpful to you or could worry you in unexpected ways.
• could reveal that some of your relatives have an increased risk for health problems

An important goal of NCGENES is to understand which decisions people make and how they decide whether or not to learn different types of non-medically actionable incidental information. This will be important because more people will be making these same decisions in the future as more clinics offer WES. For this reason, we want you to make the decision that is best for you and your family.

Write your questions and/or concerns that you would like to discuss:

A chart is located at the end of this brochure if you would like to use it to mark your decisions about whether or not to learn information from the different types.

Type A Incidental Information: Risks for Common Diseases

Variants, called SNPs (pronounced “snips”), that may slightly affect your chance for developing common conditions like heart disease, cancer, and diabetes

Facts about the information in Type A:

Everyone has a chance of getting a health problem like heart disease, cancer, or diabetes.
Some genetic variants, called SNPs (Single Nucleotide Polymorphisms), are related to this chance.

**Most people have this DNA sequence:**

A C C G C T A T G G C G C T A...

**A few people have this SNP (difference):**

A C G G C T G T G G C G C T A...

Single Nucleotide Polymorphism (SNP)

The SNPs do not cause these health problems. Instead, they are located near other, unknown genes that appear to slightly affect your chance of developing symptoms of these conditions. Although we can't test for these unknown genes, we can identify the SNP’s that are located in the same area of the genome.

Several SNPs will be examined and your pattern of SNPs for each condition will be reported. There are no proven ways to accurately interpret a specific pattern of SNPs for any of these conditions. Therefore, the interpretation of these SNPs may be inaccurate.

**Most people in NCGENES will learn that they have a slightly increased or a slightly decreased chance of getting these conditions compared to the average person.**

**Limitations of knowing this information:**

Your chance of getting these common conditions depends on many factors including your age, your sex, your environment and your family history. Many of these factors cannot be changed.

Your pattern of SNPs can only tell how your chance of getting these conditions compares to the average person. It cannot tell you about your personal risk.

If your pattern of SNP’s suggests a slightly increased risk for a disease, there are no specific actions for you and your doctor to take to decrease this risk or to prevent the disease other than usual advice given to everyone, such as eating right and exercising.

If your pattern of SNP’s suggests a slightly decreased risk for a disease, you could still get the disease.

**How to learn information from Type A:**

Call the NCGENES office (919-537-3795) to make an appointment to speak with a certified genetic counselor by phone. We will then specifically examine your WES to find your pattern of SNPs.

A genetic counselor will then call you back to report the SNPs found and discuss their meaning and possible impact on you and your family.
Type A variants will not be confirmed and cannot be placed in your medical record

SNPs are common and they are related to very small changes in your risk for very common diseases. Doctors do not yet know what these results mean and there are no specific medical actions to take based upon these results. Therefore, these variants will not be confirmed in UNC’s Molecular Genetics Laboratory, and they will not be placed in your UNC Hospitals’ electronic medical record (EMR). You will receive a written report.

What are your reasons for learning this type of information?

What are your reasons for not learning this type of information?

Type B Incidental Information: Pharmacogenomics

Variants that affect how your body responds to some medicines

Facts about the information in Type B:

Genetic variants can affect the way your body breaks down or metabolizes some medicines.
For example, some people can metabolize a blood thinner called Coumadin (Warfarin) faster than average. Other people metabolize this medicine slower than average.

People who metabolize these medicines at a different rate than average may need a different dose than the average person. However, doctors do not know how to use this information to figure out which is which is the right dose to use.

![Diagram of everyone in the population metabolizing blood thinners at different rates]

**EVERYONE IN THE POPULATION**

- Metabolize Slowly
- Metabolize Normally
- Metabolize Quickly

Most people in NCGENES will learn that their variants show that they break down these medicines at the average rate.

**Limitations of knowing this information:**

Most people do not take the medicines that are affected by these genetic variants.

Even if you do take them and learn that you have a gene variant that affects the breakdown rate, there is no definite way for a doctor to use this information to know which dose is best for you.

**How to learn information from Type B:**

Call the NCGENES office (919-537-3795) to make an appointment to speak with a certified genetic counselor by phone. We will then specifically examine your WES for variants in this group of genes.

A genetic counselor will then call you back to report the variants found and discuss their meaning and possible impact on you and your family.

**Type B variants will not be confirmed and cannot be placed into your medical record**

Variants in these genes are common and can be accurately found by WES. However, doctors still don’t know the best way to use this information. Therefore, these variants will not be confirmed in
UNC’s Molecular Genetics Laboratory, and they will not be placed in your UNC Hospitals’ electronic medical record (EMR). You will receive a written report.

What are your reasons for deciding to learn this type of information?

What are your reasons for deciding not to learn this type of information?
Type C Incidental Information:
Carrier Status for Autosomal Recessive Conditions

Variants in genes that do not usually affect your health but that increase the risk for health problems in your children and others in future generations.

Facts about the information in Type C:

Everyone has two copies of each gene. One copy is inherited from their mother and the other copy is inherited from their father. Certain variants in these genes cause health problems, but only in those people who have the variants in both copies of the gene.

People who have a variant in only one copy of the gene are called “carriers.” Everyone probably has between two to twelve of these kinds of variants.

Carriers do not usually have health problems if they have only one copy of the variant. But if their partner is also a carrier, there is a 1 in 4 or 25% chance that their child will inherit both variants (one from each parent). Children who inherit both variant will have the condition. These conditions usually cannot be prevented or cured, but they may have some treatments.

Some examples of these kinds of conditions are cystic fibrosis and sickle cell anemia. These conditions are inherited in the pattern described above called “autosomal recessive.”

![Diagram of autosomal recessive inheritance pattern](https://www.nlm.nih.gov/pubs/autosomes/autosomal-recessive-inheritance-pattern.png)

Everyone carries an average of six variants in different genes.
**Limitations of knowing this information:**

Learning that you are a carrier does **not** usually tell you about your own health. It only tells you that you have an increased chance that your children and others in future generations could have a genetic condition. In order to determine the size of this risk, both parents need to have carrier testing. Learning that you are a carrier means that others in your family could also be carriers.

WES cannot identify every variant in this group of genes. Therefore, if a variant is not found in a specific gene, it does not mean that you are definitely not a carrier. Instead, a negative result means that your chance of being a carrier is very small.

**How to learn information from Type C:**

Call the NCGENES study office (919-537-3795) to schedule a study visit. We will then specifically examine your WES for variants in this group of genes.

During your study visit, you will meet with a certified genetic counselor and/or medical geneticist to learn which variants were found. We will discuss the meaning and possible impact on you and your relatives.

**Type C variants will not be confirmed and cannot be placed into your medical record**

Everyone is expected to have many variants in this group of genes. They will not be confirmed in UNC’s Molecular Genetics Laboratory. Because only confirmed variants can be placed in your UNC Hospitals’ electronic medical record (EMR), any variants found from this group will not be placed in your EMR. You will receive a written report.

**What are your reasons for deciding to learn this type of information?**

**What are your reasons for deciding not to learn this type of information?**
Type D Incidental Information:
Risk for the Common Form of Alzheimer’s Disease

Variants in a gene called APOE that affect your risk, as compared to the average person, of getting the common form of Alzheimer’s disease

Facts about the information in Type D:

Everyone has a chance of getting Alzheimer’s disease. This disease affects your memory and it gets worse over time. There are no proven ways to prevent it, treat it, or cure it.

Three variants in a gene called APOE can affect your chance of getting Alzheimer’s disease compared to the average person. These variants are called APOE e2, APOE e3 and APOE e4. You inherit one copy of the APOE gene from your mother and one copy of the gene from your father.

As shown in the table below, if you inherit the “e2” variant from your mother and the “e2” variant from your father, you will have the “e2e2” form of the APOE gene.

<table>
<thead>
<tr>
<th>Possible APOE Variants Inherited From Your Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible APOE Variants Inherited From Your Father</td>
</tr>
<tr>
<td>e2</td>
</tr>
<tr>
<td>e3</td>
</tr>
<tr>
<td>e4</td>
</tr>
</tbody>
</table>

Most people’s APOE gene variants show that they have an average risk of getting the Alzheimer’s disease.

A few people have APOE variants that raise (e4/e4) or lower (e2/e2) their risk as compared to the average person.

Limitations of knowing this information:

Your chance of getting Alzheimer’s disease depends on many other factors including your age, your sex, your environment and your family history. Many of these factors cannot be changed.

Your APOE variants only tell how your chance of getting Alzheimer’s disease conditions compares to the average person. It cannot tell you about your personal risk.
Knowing this information does not tell you whether or not you will get Alzheimer’s disease. There are no definite actions that you and your doctor can take to use the information to help prevent disease.

**How to learn information from Type D:**

Call the NCGENES office (919-537-3795) to schedule a study visit. We will then specifically examine your WES to identify your APOE gene variants.

During the visit, you will meet with a certified genetic counselor and/or medical geneticist to learn which variants were found. We will discuss their meaning and possible impact on you and your family.

**Type D (APOE) variants will be confirmed and can be placed into your medical record**

The UNC Hospitals’ Molecular Genetics Laboratory (MGL) will confirm the APOE variants before you learn them.

You will receive a written report will be asked to decide whether or not to have these results included in your UNC Electronic Medical Record. You will sign a form about this decision

What are your reasons for deciding to learn this type of information?

What are your reasons for deciding not to learn this type of information?
Type E Incidental Information: Rare Genetic Diseases

Rare variants in genes that directly cause you to have an increased risk for a genetic disease that cannot be prevented, but that may have some treatments after symptoms develop.

Facts about the information in Type E:

These rare variants directly cause you to have a higher risk for getting an uncommon genetic disease as compared to people who do not have these variants. It is very unlikely that you will have one of these variants.

For some variants in this group, there is a low risk (less than 15%) that you will develop symptoms. Most people will never develop them. For example, variants that cause a disease called thrombophilia can lead to blood clots in some people but most people with these variants will not develop them.

For other variants in this group, there is a high risk (more than 75%) that you will develop symptoms. For example, variants that cause a disease called polycystic kidney disease lead to multiple kidney cysts. Most people with these variants will develop cysts and most will eventually need dialysis or a kidney transplant.

Most people in NCGENES will have normal results in this category because these variants are rare. That means you will probably not have one of these variants.

Limitations of knowing this information:

For many of the genes in this group, learning which variants you have does not tell you whether or not you will ever get symptoms.

Information from Category E is non-medically actionable because there are no definite actions that you and your doctor can take to use the information to help prevent disease. There may be some treatments available after symptoms develop.

It is rare for people to get any of these diseases. Also, learning that you have one of these variants will not help a doctor make decisions about how to treat the disease in you.

Knowing that you do not have one of these rare variants does not decrease your overall risk of developing a condition because these are rare causes of health problems.
How to learn information from Type E:

Call the NCGENES office (919-537-3795) to schedule a study visit. We will then specifically examine your WES for variants in this group of genes.

During your visit, you will meet with a certified genetic counselor and/or medical geneticist to learn whether or not any variants were found. If so, we will discuss their meaning and possible impact on you and your family.

Type E variants will be confirmed and can be placed into your medical record

These variants are rare but can significantly increase your risk for a serious disease. The UNC Hospitals’ Molecular Genetics Laboratory (MGL) will confirm this group of variants before you learn them.

You will receive a written report will be asked to decide whether or not to have these results included in your UNC Hospitals’ Electronic Medical Record (EMR). You will sign a form about this decision

What are your reasons for deciding to learn this type of information?

What are your reasons for deciding not to learn this type of information?
Type F Incidental Results:

Very rare variants in genes that directly cause severe and progressive diseases of the brain and nervous system that cannot be prevented and that have no effective treatments after symptoms develop.

Facts about information from Type F:

These variants directly cause very rare and severe diseases of the brain and nervous system.

Unlike the other variants described in this brochure, if you have one of these variants, it means that you will almost certainly get the disease. These diseases have no effective treatments.

In many of these diseases, people lose their memory and can’t think clearly. Some of these diseases cause paralysis. The diseases in this group get much worse over time and can cause death at a younger than average age. These diseases cannot be prevented or successfully treated.

An example of a disease in this group is a rare, inherited form of Lou Gehrig Disease (Amyotrophic Lateral Sclerosis or ALS). In this disease, the nerve cells that connect the muscles to the brain and to the spinal cord die and this damages a person’s ability to move their muscles. This disease can eventually lead to total paralysis. It cannot be prevented or effectively treated.

These diseases and the variants that cause them are very, very rare.

Most people in NC GENES will have normal results in this category because these variants are very rare. That means you will probably not have one of these variants.

Implications of knowing this information:

If you have one of these variants it means that you will almost certainly get the disease.

There are no steps for you and your doctor to take to prevent you from getting the disease.

None of these diseases can be prevented or successfully treated.

Many of the genes causing these conditions are inherited from parent to child in an autosomal dominant pattern, as shown below. If you have one of these variants, others in your family may also have a high risk of getting the disease.

Knowing that you do not have one of these rare variants does not decrease your overall risk of developing a condition because these are rare causes of health problems.
How to learn information from Type F:

Call the NCGENES office (919-537-3795) and schedule the first of two study visits.

During the first visit, you will meet with a certified genetic counselor and medical geneticist to learn more about these diseases and what it could mean for you and your family to learn this information.

If, after this first visit, you decide you definitely want to learn this information, you will need to call the office again and schedule a second visit. We will then specifically examine your WES for variants in this group of genes. During the second study visit, you will learn whether or not any of these variants were found.

**Type F variants will be confirmed and can be placed into your medical record**

These variants are very rare and cause serious and untreatable diseases. The UNC Hospitals’ Molecular Genetics Laboratory (MGL) will confirm this group of variants before you learn them.

You will receive a written report will be asked to decide whether or not to have these results included in your UNC Hospitals’ Electronic Medical Record (EMR). You will sign a form about this decision.
What are your reasons for deciding to learn this type of information?

What are your reasons for deciding not to learn this type of information?
## Chart to Record Your Decisions about Each Type

<table>
<thead>
<tr>
<th>Type</th>
<th>Description of Risk</th>
<th>Your Decision</th>
<th>Reasons For and Against</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Common Diseases</td>
<td>No</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unsure</td>
<td></td>
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<tr>
<td>B</td>
<td>Abnormal Response to Some Medications (Pharmacogenomics)</td>
<td>No</td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
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<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>C</td>
<td>Carrier Status</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>D</td>
<td>Common Form of Alzheimer’s Disease (APOE)</td>
<td>No</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>E</td>
<td>Rare Genetic Diseases</td>
<td>No</td>
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<tr>
<td></td>
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<td>Yes</td>
<td></td>
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<tr>
<td></td>
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<td>Unsure</td>
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<tr>
<td>F</td>
<td>Rare, Severe, Progressive Diseases of the Brain and Nervous System</td>
<td>No</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
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