What is a genetic test for PXE?

A genetic test is a laboratory test that may be able to tell if you have changes called mutations in the gene associated with PXE, the ABCC6 gene. If the test finds that you have two changed copies of the gene (mutations or alterations), then you are affected by PXE. If the test finds only one changed copy, then either you are a carrier (like Jack in Figure 1), or you are affected (like Paul in Figure 1) but the test at this stage of its development was unable to uncover your other mutation. If the test finds that you have no mutations, then it is very likely you don’t have PXE, or the laboratory conducting the test could not find either of your mutations. There are some mutations and alterations that have not yet been discovered by researchers.

Why choose genetic testing for PXE?

You may choose to have a genetic test for PXE to confirm a diagnosis of PXE (particularly if your symptoms are mild or not typical or your doctors are unsure of the diagnosis) or because you have a family history of PXE and want to find out if you have PXE. A genetic test can determine whether you have one copy of the changed gene (and are a carrier of PXE) or two copies and thus may develop PXE. (Carriers of PXE usually do not show any symptoms of PXE, but a skin biopsy from a carrier may show abnormalities of elastic fibers similar to, but generally milder than, those in people diagnosed with PXE. This does not mean the carrier has PXE.)
Reasons to consider genetic testing for PXE

Deciding to be tested is a personal decision that should be made in collaboration with your family and healthcare providers. You might choose genetic testing for the following reasons:

**To intervene medically:** People at a higher risk for PXE symptoms may have the option of having more frequent clinical exams, screening tests, avoiding specific risk factors, making lifestyle changes to lessen additional risk, or taking preventive measures, if available.

**To relieve anxiety:** If a person has multiple family members who have PXE that can be traced to a specific genetic mutation, then a negative test result (meaning there is no mutation) or confirming only a carrier status may give this person a sense of relief.

Additional factors to consider:

**Genetic testing has limitations, with psychological and emotional implications.**

- **Testing may cause depression, anxiety, or guilt.** If a person receives a positive test result (meaning a mutation exists), it may cause anxiety or depression about the possibility of developing PXE. Some people may start to think of themselves as sick, even if they never develop PXE International symptoms. If a person does not have the mutation when other members of the family do, this individual may experience guilt.

- **Testing may cause family tension.** In some situations, a person may feel a responsibility to tell extended family members that they have a positive test result and encourage them to be tested.

This process may lead to tension in the family.

- **Testing may provide a false sense of security.** Just because a person's genetic test result is negative (meaning no mutation was found) does not mean that person will never develop PXE symptoms.

- **Testing may provide unclear results.** A person's gene may have a unique mutation that is not known to affect risk of getting PXE. Or, the gene may have a mutation that is not detected by the available test. In either case, it may be impossible to calculate the risk of the mutation as it relates to PXE, which may lead to anxiety and uncertainty.

- **Testing is costly.** Genetic testing and counseling can be expensive, especially if it is not covered by insurance. Some people pay for testing "out of pocket" because they want complete privacy when testing for PXE.

- **Testing may cause confidentiality concerns.** Results of genetic tests may be placed in a person's medical record, where there is a chance that this information could be passed on to insurance companies, managed care organizations, or employers. Some people fear that their test results may lead to genetic discrimination. Many people who undergo genetic testing are concerned about maintaining the privacy of their genetic information. They may be unsure if they want to share test results with immediate relatives and are concerned about employment and health insurance discrimination, which could result in the loss of a job and/or insurance coverage.
What are the limitations of genetic testing for PXE?

We have not yet discovered all of the changes in ABCC6 that cause PXE. The genetic testing laboratory, GeneDx, first looks for certain common mutations in the gene. If you do not have one of these mutations, the testing laboratory will look next for a change elsewhere in the gene. If no changes are found, it is possible that the test is inconclusive. This can be confusing if you have symptoms of PXE or if you have been diagnosed based on an eye exam or skin biopsy. It is important to remember that you may have a change in ABCC6 that is not yet discovered using the laboratory test that is available today. If you chose testing, we will work to help you understand whatever results you receive.

Another limitation of genetic testing involves the meaning of these various mutations. We have not yet determined if or how the different changes in the ABCC6 gene (genotype) are associated with the severity of symptoms, called phenotype. We have collected information from over 600 individuals about their PXE phenotype. We looked at genotypes and phenotypes and could not find any direct correlation. In other words, we could not link a specific gene mutation to a specific symptom of PXE. We do know that environmental factors, such as lifestyle and diet, can have a tremendous impact on the symptoms and progression of PXE. It is also possible that other genetic factors such as “modifying genes” may affect how severe PXE is or what organs it affects. The genetic test for PXE does not test for these other factors.

Therefore, a genetic test will not be able to tell what symptoms of PXE will appear or when they will begin. The test results cannot tell you how severe the condition will be or how it will progress over time.

What does the test cost and how shall you pay for it?

The price of the test differs relative to how much work needs to be done to find the mutations in your genes. It is easier to find one of the common mutations than finding a mutation that is unique to you. Likewise, if you know the mutations of a family member, the test costs less since the laboratory, GeneDx, will be looking in a specific location for just two mutations. The costs are detailed in the box: Cost of the Test on page 4.

You can call PXE International for a free phone consultation with our board certified genetic counselor at 202.392.8948. The counselor will help you understand what it means to be tested. Once you have all of your questions answered, you can make an informed decision about whether or not to be tested. Once you determine that you are interested in testing for PXE, you will want to get preauthorization from your insurance company. The test can be quite expensive. You are permitted to pay out of pocket, if you wish, but you must have a healthcare professional order the test for you. You may order the test through our genetic counselor if you are going to pay out of pocket.

You will find a sample letter for requesting preauthorization on Page 10 of this document, or on our website at: http://www.pxe.org/testinsurance.
How Do I Make an Appointment for Genetic Counseling?
Please call 202.362.9599. Leave your name, address, email and phone number. Tell us whether you prefer daytime or evening. Our genetic counselor will get back to you within five business days.

Scenarios in which you might consider having the genetic test for PXE:
1) **You have a ‘positive’ skin biopsy** – a biopsy that was stained and revealed fragmented elastic fibers, typical skin lesions, and angioid streaks. You don’t really need a genetic test. It won’t really give you any more information since the diagnosis of PXE can be established clinically.

2) **You have skin lesions that look like those associated with PXE, but do not have eye findings, have a "negative" or non-diagnostic skin biopsy or would rather not have a skin biopsy.** A genetic test can confirm the diagnosis of PXE. However, if the test comes back negative, it is possible that it just did not find your mutations.

3) **You have peau d’orange, angioid streaks and/or retinal bleeding, but do not have skin lesions.** As above, a genetic test can confirm the diagnosis of PXE. However, if the test comes back negative, it is possible that it just did not find your mutations.

4) **You have a sibling with PXE.** You may be a carrier (50% chance, a one out of two chance), not a carrier (25% chance, a one out of four chance) or affected (25% chance). If your sibling’s mutations are known, then a genetic test can more easily find the same mutations in you, if they are present. If your sibling’s mutations are not known, the test may or may not tell you if you have PXE. If two mutations are found in your sample, then you are affected. If one mutation is found, it is likely you are a carrier, but it also may be that your other mutation was not discovered. If no mutations are found, perhaps you are not a carrier or affected, or the test did not discover your mutations.

5) **You have a parent with PXE.** You are almost certainly a carrier. In the unusual event that your other parent is a carrier, then you could be either a carrier or affected. If your parent’s mutations are known, then a genetic test will tell you with certainty if you are a carrier or affected. If your parent’s mutations are not known, the test may or may not tell you if you have PXE. If two mutations are found, then you are affected. If one mutation is found, it is likely you are a carrier, but it also may be that your other mutation was not discovered. If no mutations are found, perhaps you are a carrier or affected, or the test did not discover your mutations.

Okay, you want to be tested.
After you have received an approved preauthorization from your insurance company (try to get a written copy or
fax), or determined that you will have to pay a co-payment, or pay for all of the test costs out of pocket, you need to get the right forms and have blood collected. Follow these steps:

1. **Get the necessary forms**: You need two forms, the Sample Submission Form and the Clinical Data Form. You can use the forms included in this bulletin; you can download them from www.pxe.org/test; or you can visit www.genedx.com and search under “Tests Offered” by “Disease” (PXE) or “Gene” (ABCC6). Then download the Sample Submission Form and the Clinical Data Form.

2. **Fill out the forms**: Bring the Sample Submission Form and the Clinical Data Form to your doctor. You should fill out the Clinical Data Form together with your doctor and send it and the Sample Submission Form to the laboratory with your sample.

3. **Sample collection**: Your doctor can collect a blood sample from you for genetic testing. Or, if you would rather, you can use a cheek swab kit. You can order a cheek swab kit from GeneDx or PXE International or your doctor can order the kit and have it mailed to you.

GeneDx will look at the ABCC6 gene in your DNA and determine if there are any mutations in the gene. They will send a report to your doctor and s/he will report the results back to you. You can ask for a copy of the report, and you can also make an appointment with our board certified genetic counselor by calling 202.362.9599 and leaving your name, phone number and whether you would like a day time or evening phone appointment.

### Cost of the Genetic Test for PXE

<table>
<thead>
<tr>
<th>Service Description</th>
<th>Cost</th>
<th>Turn-Around Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing for the common mutations in a new patient</td>
<td>$500</td>
<td>Approximately 2-4 weeks</td>
</tr>
<tr>
<td>Testing for other than the common mutations in a new patient</td>
<td>$3000</td>
<td>Approximately 8-10 weeks</td>
</tr>
<tr>
<td>Testing of a relative for one specific known mutation</td>
<td>$350</td>
<td>Approximately 2-4 weeks</td>
</tr>
<tr>
<td>Testing of a relative for two specific known mutations</td>
<td>$500</td>
<td>Approximately 2-4 weeks</td>
</tr>
<tr>
<td>Prenatal diagnosis for a specific known mutation</td>
<td>$1500</td>
<td>Approximately 2 weeks</td>
</tr>
</tbody>
</table>

Prices and Turn-Around Time – *Fees are subject to change without notice*.

**Are there any risks to having a genetic test?**

When the genetic test involves only a cheek swab, there are no significant physical risks beyond those of rubbing a swab on the inside of your cheek. If it involves a blood draw, then risks can include slight pain and bruising. There is also the possibility that finding out the results of a genetic test might affect you emotionally. Finding out that you do or
do not carry PXE mutations can be emotionally difficult. You may feel confused or upset about being diagnosed with PXE.

Another risk to consider before undergoing genetic testing is the privacy of your test results. People may be concerned that they will lose their job or be unable to get health or life insurance if someone learns that they carry the mutated gene(s) for PXE. Federal legislation to ban genetic discrimination in employment and insurance is working its way through Congress. Already established, the Americans with Disabilities Act (ADA) protects Americans with disabilities from discrimination. In addition, many U.S. states prohibit health insurers from asking for or requiring genetic test results, from denying coverage on the basis of genetic tests, and from using tests to determine rates and benefits.
How is PXE Inherited?

Autosomal Recessive Inheritance

You have two copies of the PXE gene, one from your mother and one from your father. PXE is caused by changes in this gene called ABCC6. Imagine that you are the circle in Figure 1 labeled ‘You’. In this drawing, an uppercase ‘P’ stands for an ABCC6 gene without any mutations (changes) in the gene. A lower case ‘p’ stands for an ABCC6 gene with mutations that cause PXE. In this drawing, your mother and father each carry one of each. They have both passed their mutated gene to you and so you are affected by PXE. In this drawing, your mother and father each carry one of each. They have both passed their mutated gene to you and so you are affected by PXE. A colored-in circle (female) or square (male) means the person is affected. This is called autosomal recessive inheritance, and it means that it takes two mutated genes to cause a disease.

You will also notice that neither of your parents have PXE, because they have one ABCC6 gene without any mutations, and this gene functions well enough to override most of the effect of the other mutated gene. In addition, any of your siblings with two mutated ABCC6 genes are affected by PXE; and those that have at least one ABCC6 with no mutations, do not have PXE.

Let’s look at your parents’ ABCC6 gene using Figure 2 above, called a Punnett square. Your mother and father both have one ABCC6 gene with no mutation, labeled uppercase ‘P’; and they are both carriers of a mutation, labeled lower case ‘p’ in Figure 2. The figure shows the odds of passing on these genes. You can see that for each offspring, your parents had the opportunity to pass on the PXE mutation or not - so it is 25% (one out of four) likely with each pregnancy that an offspring will get two PXE mutations (pp), and be affected like you or Paul in the drawing. The odds are that fifty percent of the offspring will be carriers (‘Pp’ - like Jack in Figure 1) and 25% (one out of four) of the offspring will
have two ABCC6 genes without mutations ('PP' - like Jane in Figure 1).

You may have noticed that the family in Figure 1 does not have the 'right' percentages — the odds are that 50% of the offspring should be carriers and only 25% affected. But, the odds do not dictate results. When you flip a coin it should come up heads or tails each 50% of the time, but you know you can 'beat the odds' and have a string of heads or tails for a while. Statistically it works out, but isolated and small sequences might not fit the odds.

Now look at Figure 3. Here is another family that 'beat the odds'.

If you do not see any individuals with PXE in your family in the generations before and after you, is that unusual? No. It is very common in PXE families and in any family with a recessive disease. Most individuals have either no other affected relatives or just siblings with PXE. This is because PXE is autosomal recessive and PXE will not show up in your family again unless a carrier or affected individual marries another carrier. We see this situation in Figure 4.

When does PXE appear in more than one generation?
Two possible reasons are as follows:

A high carrier frequency. This means that there are many people in the general population with one changed copy of the ABCC6 gene. In some families, people who have PXE have had children with people who are carriers. In this situation, there is a 50% chance of having a child with PXE, but it is still autosomal recessive inheritance.

Parental consanguinity. This means that the parents of the child with PXE are related to each other. When people are related, they have a higher chance of having the same changed gene that
has been passed down to them from their common ancestor. This situation puts them at higher risk to have a child who may inherit the same changed gene and have a recessive problem like PXE.

The blood we collected from all of the donors to the PXE International Blood and Tissue Bank helped to create a genetic test for PXE.

When we began to collect blood for the PXE International Blood and Tissue Bank, blood donors naturally asked us: "What will you learn from my blood? Will you tell me what you have found? Do my children have PXE? Do my siblings have PXE? Will my grandchildren be affected?" The new genetic test for PXE will help to answer these questions.

Our research has been very fruitful over the past several years with the PXE International Research Consortium (PIRC), a group of scientists that have determined almost a hundred mutations in the ABCC6 gene that cause PXE.

Their work contributed to developing the PXE test. It was finally brought to fruition through a partnership enabled through a government program called CETT: Collaboration Education in Test Translation. This program was developed by a number of individuals, including PXE International’s executive director, to address the problems around genetic testing for rare diseases. Funded by the Office of Rare Diseases, National Institutes of Health, the program requires a laboratory, a physician/researcher and a support group to work together to create the test. Gene DX, a laboratory dedicated to rare disease testing in Gaithersburg, MD, agreed to develop the test. Dr. Lionel Bercovitch, the medical director of PXE International, is the clinician/researcher who worked to develop the test. Of course, PXE International is working on the test team as the support organization. The PXE test is a result of the Collaboration, Education, and Test Translation (CETT) Program created by the NIH Office of Rare Diseases and will be part of the ongoing work in that program. To that end, all of the information collected in the CETT tests is combined in a single database without any personal identifiers, to be used by scientists to understand PXE and other conditions better. You can learn more about the CETT program at: http://www.CETTprogram.org
# Collaboration Education and Test Translation (CETT) Program:

**Clinical Data Form** for Genetic Testing

**Pseudoxanthoma Elasticum (PXE)**

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**Patient Name:**

**Date of Birth:** 

**Today’s date:**

**Submitting physician:**

**Contact Information:**

**Sex:**
- Male
- Female

**Age:**

**Wt. lbs:** (or kg:)

**Ht. ft & in:** (or cm:)

**Ethnicity:**
- Hispanic
- Non Hispanic
- Black/African American
- American Indian
- Asian
- Caucasian
- Hawaiian/Pacific Islander
- Mixed

---

**Skin**

**Skin Lesions:**
- Yes
- No

**Lax/loose skin:**
- Yes
- No

**Areas affected:**
- Lateral neck
- Underarm
- Inside elbow
- Groin
- Behind knees
- Other – describe

**Skin biopsy performed:**
- Yes
- No

**Site of biopsy:**

**Stain used:**

**Skin biopsy results:**
- Positive
- Negative
- Inconclusive
- Not performed

---

**Eyes**

**Peau d’Orange:**
- Yes
- No

**Angioid streaks:**
- Yes
- No

**Retinal bleeding:**
- Yes
- No

**Vision loss:**
- Yes
- No

**Other eye problems related to PXE:**

---

**Other organs affected?**

**Gastrointestinal bleeding:**
- Yes
- No

**Other:**

---

**Family History**

**Affected sibling:**
- Yes
- No

**How diagnosed:**

**Affected parent:**
- Yes
- No

**How diagnosed:**

**Affected grandparent:**
- Yes
- No

**How diagnosed:**

**Affected cousin:**
- Yes
- No

**How diagnosed:**

**Other affected relative:**

**How diagnosed:**

**Other family information:**

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**Testing recommendations:** All individuals with characteristic yellow papules and/or lax redundant skin in the flexural areas (neck, axilla, antecubital or popliteal fossa, groin). All individuals with retinal angioid streaks. Individuals with siblings with confirmed PXE.