CONSENT FORM FOR CONDUCTING GENETIC TESTING
FOR THE *ENPP1* AND *ABCC6* GENES

Patient Name: _____ Patient Date of Birth: ___ ___/___ ___ ___/___ ___ ___ ___
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1. **Introduction:** You are being invited to take part in a research study because your doctor wants to test you for changes, also called mutations or variants, in the *ENPP1* and or *ABCC6* genes. Changes in the *ENPP1* gene can cause Ectonuclotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1) Deficiency, a condition which has been called Generalized Arterial Calcification of Infancy Type 1 or GACI in infancy, and/or Autosomal Recessive Hypophosphatemic Rickets Type 2 (ARHR2) post infancy. Changes in the *ABCC6* gene can cause ATP binding cassette subfamily C member 6 (ABCC6) Deficiency, a condition which has been called GACI Type 2 in infants. You can decide if you do or do not want to have the genetic test; in other words, it is entirely voluntary.

   This genetic test will look at your genetic information in the *ENPP1* and or *ABCC6* genes for changes that may explain your, your child's, or your fetus' condition. This test can also look to see if you are a carrier of a change in one of these genes. Carriers generally do not have the condition.

   We are all made up of many cells. Nearly all of these cells contain genetic information called deoxyribonucleic acid or DNA, which is information to tell our bodies how to work. We all have changes or variations in our genetic information and sometimes these changes can cause our bodies to not work correctly. Currently, some of the genetic changes that can cause disease are known, but not everything is known about all of the genetic changes that can cause disease.

   Throughout this document, you can mean you, your child or your fetus depending on the situation.

2. **Purpose of a genetic test:** This genetic test is being performed to look at your genetic information or DNA using laboratory methods that are intended to determine if the genetic condition (disease or syndrome) you, your fetus, or your family member has is due to changes in your DNA. For this test, your Healthcare Provider (HCP) has explained the recommended testing for GACI or ARHR2 is genetic testing of the *ENPP1* and/or *ABCC6* gene(s).

   GACI is characterized by a large number of calcifications (deposits of calcium) and narrowing of the arteries in the body, including of the heart. High blood pressure and heart failure are common in fetuses and infants with GACI. Calcifications can also occur in other body areas, such as joints and kidneys. GACI is frequently fatal before birth or within the first six months after birth. The cause of death is usually heart attacks or stroke. The first six months of life are considered a critical period for GACI patients; approximately half of infants with GACI do not survive beyond this period. However, the rate of death decreases substantially among patients who do survive beyond 6 months of age.

   Individuals who survive the critical period in GACI and have changes in the *ENPP1* gene can go on to develop ARHR2. In this condition, the bones do not grow in the expected way, and individuals can have bowed legs and other issues with bone growth including short stature. Pain in the bones and

joints may also occur. However, not everyone with ARHR2 has had symptoms of GACI in infancy as described above.

Individuals who survive the critical period in GACI and have changes in the *ABCC6* gene can go on to develop Pseudoxanthoma elasticum (PXE). PXE is characterized by the buildup of calcium and other minerals (mineralization) in elastic fibers, which are a part of connective tissue (tissue that binds other tissue). However, patients with PXE are not the focus of this genetic test.

GACI and ARHR2 are rare genetic conditions and therefore the exact number of people who have these conditions is unknown. However, it is estimated that the chance for GACI to occur in the general population is about 1 in 400,000 people. That means that for every 400,000 people, 1 will have GACI. The rate of ARHR2 occurrence in the general population is unknown. Researchers are trying to understand the numbers of people with these conditions and how often they occur.

The sponsor of this research is Inozyme Pharma. Inozyme is a biotechnology company developing a potential treatment for Ectonucleotide Pyrophosphatase/Phosphodiesterase 1 (ENPP1) Deficiency and ATP binding cassette subfamily C member 6 (ABCC6) Deficiency. It has engaged PreventionGenetics, LLC, a genetic laboratory, to conduct the genetic testing. PreventionGenetics does not discuss the testing process or test results with patients. PreventionGenetics can discuss results with the ordering HCP.

The purpose of this research is to identify HCPs whose patients have ENPP1 or ABCC6 Deficiency and provide information to those HCPs that may help their patients.

3. **Research Procedures:** If you agree to take part, Inozyme will obtain the results of the genetic testing from the laboratory conducting the test. The laboratory will make sure that Inozyme will not receive any information that could identify you such as your name, contact information, or date of birth. When identifiers are removed from information and replaced by a unique code, the information is called "*De-identified Data*" in the United States. In the European Union, this information is referred to as "Pseudonymized Data" because there is still a way to link your results to you. In the European Union, Pseudonymized Data are legally protected in the same way as any other personal data. In addition, in the context of the research, your HCP information will be shared with Inozyme.

   If your test is positive, Inozyme will inform your doctor about natural history studies, registries, and clinical trials available to you. Your doctor will then decide whether to provide the information to you. In addition, if you take part, Inozyme will also cover the cost of performing the test, shipping the specimen and the genetic analysis. Inozyme will not pay for the visit to your HCP or any other health professional to talk about this test. In addition, Inozyme will not pay for any procedures used to obtain a test sample. You should ask your physician if you have any questions about the cost of anything associated with this test.

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Your participation will last as long as Inozyme continues to provide information about potential research studies to your doctor.

4. The risks of this research are a breach of confidentiality.

5. The benefits of this study are that you may learn about research studies that interest you.

6. **Access to the Test Results:** The following individuals or agencies have access to your genetic test result:

   i. You or your legal guardian;
   ii. Any person specifically authorized by you or your legal guardian;
   iii. Your HCP who is ordering the test or an Authorized Agent or employee of the HCP, if they are authorized to obtain the results, provide your care, treatment or counseling, and need to know the information to perform or improve your care, treatment or counseling;
   iv. The hospital or HCP for purposes of quality assurance;
   v. Federal, state or country health agencies, as they may be authorized; and
   vi. The laboratory performing the test, PreventionGenetics, LLC.
   vii. Inozyme will be sent a monthly email from the laboratory with your results.

7. **Confidentiality:** All reasonable efforts will be made to keep your results confidential. Prevention Genetics and Inozyme have taken measures to comply with the federal Health Information Portability and Accountability Act (HIPAA) in the United States and the General Data Protection Regulation (GDPR) in the European Union (EU).

8. **Withdrawal of your consent:** Your participation in this research is voluntary. You have a right to withdraw your consent for Inozyme to get your genetic results. If you wish to withdraw your consent, notify your HCP. However, once the genetic results have been shared with Inozyme, there is not a link to the results and your name, and your request to withdraw your consent cannot be honored. There will be no penalty or loss of benefits if you don't want to participate or wish to withdraw your consent. Specifically, your decision to not take part in this program or withdraw will not affect your ability to have genetic testing. However, you will not receive a genetic test for free if you decide not to sign this Consent Form. Not taking part or withdrawing will not affect your ability to have a genetic test in general, however it will not be free through this program.

9. **Questions:** If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the HCP who ordered the genetic test. This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at (800) 232-9570, or at info@neirb.com if:

   - You have questions, concerns, or complaints that are not being answered by the research team.

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- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

10. **Consent**: I hereby consent to participate in testing described above. By signing this consent, I acknowledge that:
    - I have received, read and understand the previous written explanation of this research and it has been explained to me verbally by my HCP.
    - I understand that I can revoke my consent at any time without any effect on medical care without stating the reasons. If I decide to withdraw my consent, I understand that I need to tell the HCP who ordered the test.
    - I understand that the laboratory will provide only my results (not my name or other information that could identify me), and the name and contact information of my HCP to Inozyme so they can contact the ordering HCP with information that might be of interest to me including, but not limited to, natural history studies, registries, and clinical trials. However, I understand that my HCP is under no obligation to provide the information to me and I am under no obligation to participate in any of the options.

For individuals in the European Union (EU) only

1) The Sponsor for this research, Inozyme Pharma Inc., 700 Technology Square, Cambridge, MA 02139, United States, is the "*controller*" of my personal data to the extent that they are collected and used for the purposes of this research. As the controller of my personal data, the Sponsor will be legally responsible for what happens to my data.

2) Measures will be taken to keep my personal data confidential, and to avoid that my data are actually disclosed to the Sponsor. To that end, my personal data will be encoded or "*pseudonymized*" and no identifiable information about me will be disclosed to the Sponsor.

3) My Pseudonymized Data will be:

- Used only for purposes of conducting the research as described in this Consent Form. **For this, the Sponsor relies on my explicit consent to the use of my data**;

- Shared with the data recipients described in section 6 of this Consent Form. Some of these data recipients are established in countries outside of my country of residence, such as the United States, where applicable laws may provide a different level of privacy and data protection compared to the laws in my country of residence. **I hereby consent to these data transfers**; and

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- Kept for a maximum of 2 years after the discontinuation of the genetic testing program or the discontinuation of all development programs targeting ENPP1 or ABCC6 deficiencies, whichever is later, to make it possible to link my data back to me in the future.

4) I can exercise certain data protection rights. In particular, I have:

- The right to withdraw my consent to the collection, use and disclosure of my data. In this case, no new data about me will be collected for purposes of the research. However, the data that were already collected will continue to be used in order to ensure the integrity of the research;

- The right to access, rectification and deletion of my personal data, subject to limitations provided for in law. If I wish to withdraw my consent or exercise my rights, I can contact my physician/HealthCare Provider, who can relay my request to the Sponsor, if required; and

- The right to lodge a complaint with the authority responsible for privacy and data protection in my country of residence, if I have concerns about the collection and use of my personal data. A list of these authorities at EU Member State level is available here: http://ec.europa.eu/justice/data-protection/article-29/structure/data-protection-authorities/index_en.htm

☐ **BY CHECKING THIS BOX, I UNDERSTAND THE INFORMATION ABOVE AND GIVE MY CONSENT TO THE COLLECTION AND SHARING OF MY DATA AS DESCRIBED IN THIS CONSENT FORM, INCLUDING TRANSFERS OF MY DATA TO THE UNITED STATES.**

11. Signatures

PATIENT/PARENT/LEGAL GUARDIAN

_____ _____
Signature of Patient or Parent or Legal Guardian Date

_____
Printed Name of Patient or Parent or Legal Guardian

If Legal Guardian, indicate relationship to the patient: _____

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PHYSICIAN/HEALTHCARE PROVIDER SIGNAGTURE

By signing this form, I _____ (name of ordering healthcare provider) acknowledge that I:

1. have explained the purpose of the genetic testing for individual, carrier screening or prenatal testing as appropriate for the scenario. I have also explained the risks, benefits and limitations of the genetic tests and the implications of the results to the patient or parent or legal guardian. I have given them the opportunity to ask questions and answered all their questions. I have provided a copy of this document to them.

2. consent to both PreventionGenetics and Inozyme collecting and using my contact details (including my name and location data) so Inozyme can provide to me information about Inozyme's programs including, but not limited to, natural history studies, registries and clinical trials related to GACI and ARHR2 that I can choose to share with my patient. I will not provide Inozyme with any identifiable patient information and am in no way obligated to provide any information provided from Inozyme to the patient.

   If I am a Physician/HCP in the EU: I understand that PreventionGenetics and Inozyme are established in the United States, where applicable laws may provide a different level of privacy and data protection compared to the laws in my country of residence. **I hereby consent to these data transfers.** I can withdraw my consent by contacting PreventionGenetics and Inozyme.

3. take responsibility of the appropriateness of the requested testing. I verify that the eligibility criteria have been met for the appropriate scenario below:

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a. A sample obtained from an individual who meets all the appropriate eligibility criteria for either GACI or ARHR2 as follows:

For individuals suspected of having **GACI**:	For individuals suspected of having **ARHR2**:
☐ If a plasma or urine PPi result is available, the result is less than 50% of normal. ☐ The individual has serious or life-threatening symptoms (as listed in the last line of this list below) within the first 6 months of life, and if currently older than 6 months of age, had a peak in their serious or life-threatening symptoms within the first 6 months of life. ☐ The individual has or has had arterial calcifications within the first 6 months of life for which twin-to-twin transfusion and sickle cell anemia has been excluded as the cause. ☐ The individual has or has had hypertension, respiratory difficulties, cardiac insufficiency, myocardial infarction (MI), or failure to thrive (FTT) within the first 6 months of life.	☐ If a plasma or urine PPi result is available, the result is less than 50% of normal. ☐ The individual has a current or past clinical diagnosis of rickets. ☐ Other causes of rickets, other than *ENPP1* mutations, have been excluded including, but not limited to, Vitamin D deficiency, and genetic mutations in other genes known to cause rickets including the *FGF23*, *PXE*, and *DMP1* genes.

b. For carrier screening, one of the following must be true:

☐ The individual has a previous child or pregnancy with a clinical diagnosis of GACI or ARHR2 for which genetic testing was not performed

OR

☐ Suspicion of GACI in a current pregnancy.

c. For prenatal testing, call Inozyme's Chief Medical Officer or designee to discuss the information indicating a suspicion of GACI. Inozyme will then determine if genetic testing under this free program is appropriate and approved.

_____ _____
Signature of Ordering Physician/HCP Date

_____
Printed Name of Ordering Physician/HCP

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