Protocol Cover Page

Title: Familial Hyperlipidemia Family Registry

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Protocol: Familial Hyperlipidemia Family Registry
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I. Hypothesis and Specific Aims

If a child from the Healthy Hearts and Minds education and screening program is found to have a genetic marker for familial hyperlipidemia, immediate family members are offered genetic testing at no charge to identify those at high risk for cardiovascular disorders and those who carry the genetic markers. If identified early, the risk for cardiovascular disease can be greatly modified by early and proper treatment.

The aim of the study is to gauge the impact of large-scale surveillance testing to identify those with the disorder and improve clinical care. This impact is both in disease prevention and in lessening the cost of long-term care from premature cardiovascular disease.

II. Background and Rationale

UCHealth Healthy Hearts and Minds education and screening program routinely screens 5th, 7th, and 10th graders for lipid and blood pressure status on an annual basis. Children with cholesterol levels greater than 200 mg/dl have been invited to participate in a Familial Hyperlipidemia protocol to identify individuals/families with genetic markers for lipid disorders.

Familial hyperlipidemia has four primary genetic types – LDL, LDLR, PCSK9 and Apo lipoprotein B. Individuals with familial hyperlipidemia, either heterozygote or homozygote, are at increased risk for cardiovascular events starting early in life. Approximately 1 in 300-500 people have the heterozygote genetic profile, where as a homozygous genetic profile is very rare at 1 per one million. The cardiovascular risk for heterozygotes is increased 5–10 times over the normal population and the process begins much earlier in life. If these individuals are identified early, they have a greater than 80% chance to decrease their long-term risk of cardiovascular disease and have risks similar to the normal population.

Recent evidence show that a small percentage of relatives pursue follow-up testing despite having a 50% risk of having the same variant. Reasons for not pursuing the testing include lack of knowledge about the potential disease risk, family communication barriers, lack of access to genetics services, and cost of testing.

Healthy Hearts and Minds partnered with Invitae to utilize their family variant testing. Invitae offers a no charge genetic test to biological family members for the variant that the biological related child tested positive for. Invitae provides no cost testing as a

commitment to lowering barriers to genetic testing and to increase access to genetic information that can help family members make informed health decisions.

III. Research Methods

a. **Outcome measures**: Children from the Healthy Hearts and Minds education and screening program who have been identified as having elevated cholesterol >200 mg/dl will be invited to be tested for genetic markers of Familial Hyperlipidemia. If positive for LDL, LDLR, PCSK9 or Apo lipoprotein B, immediate family members will be offered free lipid profiles, free genetic testing and referral to appropriate consultation for treatment of lipid disorders in adults or children. Family trees will be developed to ensure contacts are complete so each individual is allowed access to the lipid and genetic testing. The registry will catalogue family trees of the affected families to allow better identification of those who have the variant.

   General health and medical information will be collected. A health questionnaire relating to cardiovascular disease and cardiovascular risk factors will be filled out for each biological family member (Appendix A). This will include questions about heart disease, high blood pressure, elevated cholesterol, and health habits. REDCap will be utilized to administer questionnaires. These forms will be collected, uploaded and stored in secure databases that only the research team will have access via their secure login and password. All data will be de-identified when presented outside of study.

b. **Description of population to be enrolled:**

   Inclusion criteria: Any biological relative of the child who had a positive result for familial hyperlipidemia that participated in the "School-based Education and Screening Program with Lipid Screening as a Means to Identify Familial Hyperlipidemia study" (IRB 20-6010) will be invited to enroll. Children from 6 months old to adults of any age may enroll.

   As the genetic test will be provided by Invitae for no cost to all biological family members of the identified child as part of the family variant testing program, the number of genetic tests performed is not restricted by budgetary constraints. In addition, the limitation for numbers to enroll is based on the number of children from the familial hyperlipidemia study that are discovered to have a positive result for the gene and the number of biological relatives that request to receive a free genetic test. It is estimated that 10-20% (approximately 10-20 children) who enroll in the IRB 20-6010 study will be positive for familial hyperlipidemia and therefore no more than 5,000 biological relatives will enroll in this study.

Exclusion criteria: A participant may not enroll in the study if they are not biologically related to a child who was informed they have a positive result for familial hyperlipidemia from the IRB 20-6010 research study.

c. Study Design and Research Methods:

Children from the Healthy Hearts and Minds education and screening program identified as having elevated cholesterol >200 mg/dl will be tested for genetic markers of Familial Hyperlipidemia as part of the IRB 20-6010 study, which began in August 2022. Only the biological family members of a child with a positive test will be included in the study.

It is the responsibility of that child's parent or guardian to contact extended biological family members and inform them of their ability to receive their own family genetic testing kit. A flyer (Appendix B) will be provided which they can send to their immediate family members that will inform them on how to receive the free genetic test.

The family members have 150 days from the child's positive result to receive a free genetic test from Invitae. Once they contact the Healthy Hearts and Minds Research team, they will schedule their study visit to perform the genetic test and lipid panel. If the biological family member has already completed a genetic test or lipid panel, they can provide us with the testing results.

If a participant already performed the genetic test at any time point, they can provide their results for LDL, LDLR, PCSK9 and Apo lipoprotein B.

A translator will be made available and all materials will be translated by a certified medical translator if needed.

Study visits: Visits will occur at the Healthy Hearts and Minds office located at 3855 Precision Drive, Suite 180, Loveland, Colorado. A visit will last approximately 30-45 minutes. If the participant chooses, they may opt have the study kit mailed to them in order to perform the buccal swab at their home.

Study duration: Enrollment for the study will continue until 150 days after the final child that enrolls in IRB 20-6010 has their familial hyperlipidemia test resulted. Anticipated enrollment end date is July 30, 2025.

Study visit one:
Consent process
The consent form will be reviewed and signed by the adult participating. If a child is participating, the child will be provided an assent to read over and agree to participate as well. Everyone will be able to ask questions regarding the study. The signature of only one parent or guardian will be required for a child to participate. The Guidance on the Genetic Information Nondiscrimination Act (GINA) will be

reviewed. A certified genetic counselor, provided by Invitae, will be available to answer questions if needed. The use of e-consent will be used for this study via REDCap. The consent conversation with the potential participant will be in person or via Microsoft Teams. An exact copy of the informed consent will be loaded into REDCap and used in place of the paper form. The delegated staff member conducting the informed consent will do so in the same manner as providing informed consent as they would a paper copy. The delegated staff member conducting the informed consent and the participant will electronically sign the informed consent in REDCap. A copy of the signed e-consent will be emailed/mailed after based on their preference. The consent conversation will not change, the e-consent will be on a tablet. A paper consent form will be available if the participant's requests.

Sample collection

Post consent, the health history questionnaire will be obtained. In addition, genetic testing for familial hyperlipidemia and a lipid panel will be performed as outlined below:

- **Invitae genetic testing kit:** A buccal cheek swab will be utilized to collect the sample. The participant will be required to not have had any food or drink 30 minutes before the cheek swab. If the participant has previously performed the test for LDL, LDLR, PCSK9 and Apo lipoprotein B, they can opt out of the buccal swab and provide a copy of their familial hyperlipidemia results.
- **A lipid panel:** A finger stick utilizing the CardioChek Plus analyzer will be used to collect the sample. The test utilizes capillary blood and will provide results for HDL (high density lipoprotein), LDL (low density lipoprotein), and triglycerides. If the participant has already performed a lipid panel in the previous year, then they can opt out of the finger stick and provide a copy of their recent lipid panel results.

Results will be provided to the family when processed and available in approximately 4-12 weeks. The results will also be scanned and entered into the child's electronic medical records (EMR). A copy of the genetic test results can be forwarded to the child's primary care provider if requested. All participants will be offered access to clinical care for their lipid abnormalities, either through Cardiology or Pediatrics. Cost of care will be through their insurance carrier.

D. Description, Risks, and Justification of Procedures and Collection Tools.

There are no significant risks from this study. For the genetic test, there may be a slight discomfort with the cheek swab. Staff will utilize CardioChek devices and collect blood with a small finger stick blood sampling method. Risks for this capillary blood sampling are minimal, but include potential discomfort, bruising and infection.

Proper blood safety standards will be followed to minimize any potential participant and screener risk.

E. Potential Scientific Problems. There are no factors that could threaten our ability to obtain meaningful generalizable knowledge other than hesitation by a family to bring their child in to participate in a study during a pandemic may confound our sample.

F. Data Analysis Plan. Data from the family members will be tabulated and analyzed to create a family tree using R Studio and excel. Percent of family members tested who have familial hyperlipidemia will be calculated as well as estimated health care cost saving with early identification of families with the disorder.

G. Summarize Knowledge to be Gained:

Knowledge gained will occur regarding the impact of large-scale surveillance testing to identify those with the disorder. This impact is both in disease prevention and in lessening the cost of long-term care due to premature cardiovascular disease.

H. References.

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Appendix A. Health Questionnaire

1. Your Name _____

2. Relationship to identified family member *(ex. Mother, father, grandfather, aunt, brother, niece, etc.)* _____
   (Check box to indicate which side of the family.) Paternal _____ Maternal _____

3. Age _____
4. Gender _____
5. Ethnicity _____
6. BMI (Weight/Height) _____
7. Lipid results - date_____

   Cholesterol _____

   HDL _____

   LDL _____

   Triglycerides _____

7. CVD Risk factors _____
8. CV disease _____
9. Other Associated Family Members _____

   a. _____

   b. _____

   c. _____

   d. _____

Appendix B. Recruitment Flyer

UCHealth Healthy Hearts and Minds

Familial Hyperlipidemia genetic testing opportunity

You qualify to receive a genetic test from Invitae to determine if you have Familial Hyperlipidemia (FH) at **no cost**.

What is FH?

Familial Hyperlipidemia (FH) means you inherited a gene from a parent that may cause a condition that causes you to have too much fat (cholesterol) in your blood. This condition may increase the risk of cardiac events such as hardening of the arteries anywhere in the body which can result in heart attacks, strokes, and death.

Why do I qualify?

A biological relative recently participated in a research study and learned that they have the gene for FH. Finding out if you have the gene may help you and your physician determine proper treatment.

How do I get the free genetic test?

You have 150 days from this date_____ to claim your free genetic test.
You can call 970-624-1589 or email FamilyProgram@UCHealth.org.