A Community-Based Approach to Overcoming Barriers to Cascade Screening for Long QT Syndrome

NCT03783975

UNIVERSITY of MARYLAND BALTIMORE

Date: Tuesday, July 19, 2022 3:58:14 PM Print Close

HP-00081981 Introduction Page_V2

Introduction Page

1 * Abbreviated Title:
KCNQ1 Cascade Screening

2 * Full Title:
A Community-Based Approach to Overcoming Barriers to Cascade Screening for Long QT Syndrome

3

* Select Type of Submission:

- (●) **IRB Application**
- ( ) Humanitarian Use Device (for FDA approved Indication & non-research purposes ONLY)
- ( ) Single Patient Expanded Access (pre-use)
- ( ) Single Patient Emergency Use (post-use)
- ( ) Unsure if this proposal requires IRB review (Not Human Subject Research)

Note: The Type of Submission cannot be changed after this application has been submitted for review.

4 Original Version #:

ID: VIEW4DF8709A33C00
Name: v2_Introduction Page

HP-00081981 Research Team Information_V2

Research Team Information

1 * Principal Investigator - Who is the PI for this study (person must have faculty status)? ***Faculty status is defined as being a full-time (>51% effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.***
Amber Beitelshees

CITI Training: ID00005662

1.1 * Does the Principal Investigator have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Susan Shaub

CITI Training: ID00000100

2.1 Does the Point of Contact have a potential conflict of interest, financial or otherwise, related to this research?
○ Yes ● **No**

3 Other Team Members - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

	Name	Edit Submission	cc on Email	Research Role	Has SFI?	CITI Training
View	Cynthia Rohrer	no	no	Research Team Member	no	
View	Charlene Wolford	no	no	Research Team Member	no	
View	Verna Fisher	no	no	Research Team Member	no	ID00012359
View	Ada Stoltzfus	no	no	Research Team Member	no	
View	Devyani Chowdhury	no	no	Research Team Member	no	
View	Karen Howk	no	no	Research Team Member	no	ID00010138
View	Kathleen Ryan	no	yes	Research Team Member	no	ID00001973
View	Marla Riehl	no	no	Research Team Member	no	ID00011510
View	Tracy Broderick	no	yes	Research Team Member	no	ID00010978
View	Diane Montgomery	no	no	Research Team Member	no	
View	Elizabeth Streeten	yes	no	Sub-Investigator	no	ID00008783
View	Susie Fisher	no	no	Research Team Member	no	ID00000326
View	Elizabeth Shaub-Zehr	no	no	Research Team Member	no	ID00001063
View	Marian Stoltzfus	no	no	Research Team Member	no	
View	Naomi Esh	no	no	Research Team Member	no	
View	Dawn Fox	no	no	Research Team Member	no	ID00003521
View	Esther Smucker	no	no	Research Team Member	no	
View	Sylvia King	no	no	Research Team Member	no	ID00007644
View	Anna Esh	no	no	Research Team Member	no	
View	Toni Pollin	yes	yes	Sub-Investigator	no	ID00004421
View	Barbara Stoltzfus	no	no	Research Team Member	no	ID00008418
View	Hanna King	no	no	Research Team Member	no	ID00006538

View	Yue Guan	no	yes	Sub-Investigator	no	
View	Kristin Maloney	no	no	Sub-Investigator	no	ID00004277
View	Melanie Daue	yes	yes	Research Team Member	no	ID00001846
View	Verna Petersheim	no	no	Research Team Member	no	ID00008100
View	Maryann Drolet	no	no	Research Team Member	no	ID00008952
View	Kathleen Palmer	yes	yes	Research Team Member	no	ID00005930
View	Katie King	no	no	Research Team Member	no	ID00011963
View	Denise Weiss	no	no	Research Team Member	no	
View	Katie Kauffman Stoltzfus	no	no	Research Team Member	no	
View	Hilary Whitlatch	no	no	Sub-Investigator	no	ID00002715
View	Lavina Ebersol	no	no	Research Team Member	no	
View	Emma Beiler	no	no	Research Team Member	no	
View	Malinda Zook	no	no	Research Team Member	no	ID00013102
View	Heather Bossie	yes	yes	Research Team Member	no	ID00013237
View	Corey Snyder	no	yes	Research Team Member	no	

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

ID: VIEW4DF85C16F2800
Name: v2_Research Team Information

HP-00081981 Resources_V2

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

1 * Describe the time that the Principal Investigator will devote to conducting and completing the research:
Dr. Beitelshees will devote approximately 20% effort toward conducting and completing this research.

2 * Describe the facilities where research procedures are conducted:
This research will be conducted at the University of Maryland, the Amish Research Clinic, and at the participants' homes. The Amish Research Clinic is located in Lancaster, PA. It consists of over 3,300 square feet of clinical, examining/procedure rooms, and fully equipped clinical laboratory for sample processing and storage. For fieldwork, there are 5 vans and a recreational vehicle outfitted to do clinics in the community.

3 * Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:
There are no significant psychological negative effects expected as a consequence of research participation. Research staff are trained in the management of complications. The Principal Investigator and physician co-investigators are available to manage adverse events related to the study.

4 * Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:
All of the research team members are oriented to the protocol procedures and responsibilities according to their respective roles on the project. They will review the IRB-approved protocol and associated documents and will participate in a series of team and individual study meetings appropriate to key research team members.

ID: VIEW4DF83CB976400
Name: v2_Resources

Sites Where Research Activities Will Be Conducted

1 * Is this study a:

- ○ Multi-Site
- ● **Single Site**

2 * Are you relying on an external IRB (not UM) to be the IRB of Record for this study?

○ Yes ● **No**

3 * Are any other institutions/organizations relying on UM to be the IRB of Record for this study?

○ Yes ● **No**

3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date

There are no items to display

4 * Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)

○ Yes ● **No**

5 Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project)

○ Yes ● **No**

6 * Institution(s) where the research activities will be performed:

- ☐ University of Maryland, Baltimore
- ☐ University of Maryland, Upper Chesapeake Kaufman Cancer Center
- ☐ VAMHCS
- ☑ **UMB School of Medicine**
- ☐ Marlene and Stewart Greenebaum Cancer Center
- ☐ University Physicians Inc.
- ☐ Shock Trauma Center
- ☐ General Clinical Research Center (GCRC)
- ☐ Maryland Psychiatric Research Center (MPRC)
- ☐ Johns Hopkins
- ☐ International Sites
- ☐ UMB Dental Clinics
- ☐ Center for Vaccine Development
- ☐ Community Mental Health Centers
- ☐ Private Practice in the State of Maryland

- [ ] Institute of Human Virology (IHV) Clinical Research Unit
- [ ] Joslin Center
- [ ] UMB Student Classrooms
- [ ] National Institute of Drug Abuse (NIDA)
- [ ] National Study Center for Trauma and EMS
- [ ] Univ of MD Cardiology Physicians at Westminster
- [ ] Nursing Homes in Maryland
- [ ] University of Maryland Biotechnology Institute
- [ ] Maryland Department of Health
- [ ] Maryland Proton Treatment Center
- [ ] Mount Washington Pediatric Hospital
- [ ] Institute of Marine and Environmental Technology (IMET)
- [x] **Other Sites**
- [ ] University of Maryland Medical System (Select below)

ID: VIEW4DF870DF2C000
Name: v2_Sites Where Research Activities Will Be Conducted

HP-00081981 Other Sites_V2

Other Sites Where Research Activities Will Be Conducted

You selected "Other Sites," "Private Practice," “Community Mental Health Centers,” and/or “Nursing Homes in Maryland” as a site where research will be conducted.

3.1 * Specify the name of the site(s):
Amish Research Clinic, Lancaster, PA

3.2 * Contact Person(s) for Other Site:
Susan Shaub, Nurse Coordinator

3.3 * Phone (if no phone available, input "none"):
717-392-4948

3.4 * Email Address (if no email available, input "none"):
sshaub@som.umaryland.edu

ID: VIEW4DF8712DB5800
Name: v2_Other Sites Where Research Activities Will Be Conducted

HP-00081981 Funding Information_V2

Funding Information

1 * Indicate who is funding the study:

- [x] **Federal**
- [ ] Industry
- [ ] Department / Division / Internal
- [ ] Foundation
- [ ] Private
- [ ] State Agency

2 * What portion of the research is being funded? (Choose all that apply)

- [ ] Drug
- [ ] Device
- [x] **Staff**
- [x] **Participant Compensation**
- [x] **Procedures**
- [ ] Other

3 Please discuss any additional information regarding funding below:

ID: VIEW4DF85DF452400
Name: v2_Funding Information

HP-00081981 DHHS Funded Study_V2

DHHS Funded Study

You indicated that this is a Federally funded study.

1 * Is this study sponsored by a Department of Health and Human Services (DHHS) agency?

● **Yes** ○ No

2 You may upload any grant documents here:

Name	Created	Modified Date
KCNQ1 R21(0.01)	7/17/2018 3:22 PM	7/17/2018 3:22 PM

ID: VIEW4DF87B9560800
Name: v2_DHHS Funded Study

HP-00081981 Federal Angency Sponsor Contact Information_V2

Federal Agency Sponsor Contact Information

You indicated that this is a Federally funded study.

1

* Agency Name:
National Institutes of Health, National Human Genome Research Institute

* Address 1:
6700B Rockledge Drive, MSC 6908

Address 2:
Building 6700B, Room 3142

* City:
Bethesda

* State:
MD

* Zip Code:
20892

* Contact Person:
David Kaufman

* Phone Number:
301-594-6907

* Federal Agency Email:
mintzerk@nhlbi.nih.gov

Grant Number 1 (if applicable):
R21HG010412- OR - Check here if Grant 1 is not assigned a number. ☐

If Grant 1 has no number, please provide the following information:
Title of Grant 1:
A Community-Based Approach to Overcoming Barriers to Cascade Screening for Long QT Syndrome
PI of Grant 1:
Amber Beitelshees

Grant Number 2 (if applicable):
- OR - Check here if Grant 2 is not assigned a number. ☐

If Grant 2 has no number, please provide the following information:
Title of Grant 2:

PI of Grant 2:

Grant Number 3 (if applicable):
- OR - Check here if Grant 3 is not assigned a number ☐

If Grant 3 has no number, please provide the following information:
Title of Grant 3:

PI of Grant 3:

Grant Number 4 (if applicable):
- OR - Check here if Grant 4 is not assigned a number. ☐

If Grant 4 has no number, please provide the following information:
Title of Grant 4:

PI of Grant 4:

HP-00081981 Research Protocol_V2

Research Protocol

1 * Do you have a research protocol to upload?

- ○ Yes
- ● **No, I do not have a research protocol and will use the CICERO application to enter my study information**

2 If Yes, upload the research protocol:

Name	Created	Modified Date
There are no items to display		

ID: VIEW4E00563F8D000
Name: v2_Research Protocol

HP-00081981 Risk Level_V2

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

- (●) **Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.**
- ( ) Greater Than Minimal - Does not meet the definition of Minimal Risk.

ID: VIEW4E02805225800
Name: v2_Risk Level

HP-00081981 Type of Research_V2

Type of Research

1 * Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):

- [ ] Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.
- [ ] Evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.
- [ ] Use of device(s) whose use is specified in the protocol
- [x] **Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).**
- [x] **Sample (Specimen) Collection and/or Analysis (including genetic analysis).**
- [x] **Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).**
- [ ] None of the above.

2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

(●) **Yes** ( ) No

ID: VIEW4E0280569E000
Name: v2_Type of Research

HP-00081981 Lay Summary_V2

Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

The Amish Complex Diseases Research Program of the University of Maryland identified a mutation in the KCNQ1 gene, a gene known to cause Long QT Syndrome (LQTS). LQTS is associated with an increased risk of fainting (syncope) and sudden death. Beta blocker medications have been shown to reduce the risk of syncope and sudden death in LQTS by 70-90%. Therefore, identifying a mutation known to cause LQTS can lead to treatment that significantly reduces an individual's risk of serious cardiac events.

The KCNQ1 gene mutation is common in the Amish, present in 1/45 individuals as opposed to the general population where mutations in KCNQ1 are seen in about 1/2000. Of 5988 Amish individuals who have participated in our research studies carried out over the past 20 years, 140 of them have this KCNQ1 variant. To date, 88 individuals have participated in a return of results study (referred to here as "ROR" study) for clinical confirmation of the mutation, collection of clinical information, genetic counseling, and recommendations for treatment. Genetic counseling includes recommendations for all first degree relatives (who are at 50% risk of having the KCNQ1 mutation) to undergo genetic screening. This is known as "cascade testing". Cascade testing would involve going to the Clinic for Special Children and obtaining the genetic test via a blood sample for $50 per test. Identifying family members who are positive for the KCNQ1 mutation would allow counseling for treatment recommendations to help prevent future cardiac events. It is known that very few family members of mutation carriers do cascade testing, but the reasons for this are not completely known. Inconvenience and cost are felt to be some of the important reasons.

The current study will evaluate the ethical, legal and social impacts of patients receiving genetic results and will assess whether providing free genetic testing in a very convenient manner (in-home, saliva collection) will improve uptake of cascade testing.

Aim 1: Individuals who participated in the ROR study (probands) and their first degree blood-related family members will be invited to participate. All probands will be mailed a consent letter describing the intervention, a survey, a response card and a copy of the family invitation letter. With the probands permission, invitation letters will be mailed to their first degree relatives to offer study participation including free, saliva-based genetic testing and completion of surveys. The proband can decide to enroll their minor children who still live at home in the cascade screening.

Our primary outcome addresses the question of whether our simplified cascade screening intervention improves uptake of screening. Our secondary outcomes assess whether, with access to simplified screening (1) probands will tell more family members- who may or may not choose to get screened, (2) informed family members are more likely to get tested, and (3) identifying more individuals with the KCNQ1 variant actually results in more beta-blocker prescriptions since the Amish typically take very few prescription medications. We will compare these outcomes before the implementation of our intervention (the 'traditional' cascade screening period) and after (the 'simplified' cascade screening period). The tertiary outcomes are demographic characteristics associated with uptake of cascade screening or uptake of preventative therapy.

Aim 2: A subset of 30 probands and 45 family members will undergo in-depth interviews in order to assess their perspectives on receiving the results and undergoing cascade screening. This aspect of the study is particularly important because of the nature of our pre-intervention/post-intervention study design. By gathering qualitative data on why participants did or did not undergo cascade screen we can discern whether it was the simplified screening approach or whether it was the second reminder to get screened, or some other aspect of the study design. Our interviews will assess how the return of results process impacted participants, how cascade screening impacted participants, why or why not participants chose to undergo screening, what were the barriers to undergoing screening, and why or why not participants followed recommendations for beta-blocker therapy.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

HP-00081981 Justification Objective Research Design_V2

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

This study will evaluate the ethical, legal and social impacts of patients receiving genetic results and will assess whether providing free genetic testing in a very convenient manner (in-home, saliva collection) will improve uptake of cascade testing.

The objectives of the protocol are to: (Aim 1) valuate the uptake of cascade screening and preventative therapies before and after the implementation of a simplified screening process and (Aim 2) assess proband and family member perspectives about the return of research results and cascade screening for the KCNQ1 Thr224Met variant. We will conduct a mixed methods study in the Old Order Amish community where the KCNQ1 variant is enriched over 100,000-fold compared to other populations. The intervention will offer free, saliva-based genetic testing for family members of probands. The rate of uptake of testing and preventative therapy will be compared before (i.e. when 'traditional' $50 blood-based testing was available to family members) and after the intervention is implemented (i.e. when 'simplified' free, in-home, saliva-based testing was available).

Aim 1 - The primary outcome is the rate of uptake of cascade screening before ('traditional') versus after ('simplified') the intervention. The secondary outcomes include: extent of disclosure of genotype results to family members before and after the intervention, proportion of informed relatives who get screened before and after the intervention, and the uptake of appropriate preventative care (e.g. seeing a cardiologist and/or taking beta-blocker). The tertiary outcomes are demographic characteristics associated with uptake of cascade screening or uptake of preventative therapy.
Aim 2 - We will also assess qualitative themes surrounding the return of results process and cascade screening using interviews.

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

This study will use mixed methods to evaluate the rate of uptake and impact of cascade screening and preventative therapies for carriers of the KCNQ1 mutation before and after our intervention. Our intervention will offer free, saliva-based cascade screening for first-degree family members of probands.

Aim 1: Prior to the start of our intervention, all probands will be mailed a consent letter describing the study, a questionnaire, a response card and a copy of the family invitation letter. The questionnaire will capture data on the period of time since their return of results, including, the extent to which they shared results with family members, health behaviors (i.e. are they taking preventative therapy, if indicated) and how the results have impacted them. With the proband's permission, invitation letters will be mailed to their first degree relatives to offer study participation including the intervention (free, in-home, saliva-based genetic testing) and completion of questionnaires about their experiences with genetic testing. The proband can decide to enroll their minor children who still live at home in the cascade screening (Screening only for children under age 18 with specified consent/assent). We will offer the intervention for approximately 9 months, then we will repeat the mailed questionnaires assessing uptake, disclosure, health behaviors, and general impact of the intervention.

We will compare outcomes before the implementation of our intervention (the 'traditional' cascade screening period) and after (the 'simplified' cascade screening period). Our primary outcome addresses the question of whether our simplified cascade screening intervention improves uptake of screening. Our secondary outcomes assess whether, with access to simplified screening (1) probands will tell more family members, who may or may not choose to get screened, (2) informed family members are more likely to get tested, and (3) identifying more individuals with the KCNQ1 variant actually results in more beta-blocker prescriptions since the Amish typically take very few prescription medications. The tertiary outcomes are demographic characteristics associated with uptake of cascade screening or uptake of preventative therapy.

Aim 2: Over the course of the intervention, in-depth interviews will be conducted in a subset of 30 probands and 45 family members in order to assess their perspectives on receiving the results and undergoing cascade screening. All family members who have been contacted by a proband will be eligible regardless of mutation carrier status and whether or not they chose to get screening. We will enroll approximately 15 probands who shared their genetic results with a family member, 15 probands who did not share, 15 family members who were screened and are mutation positive, 15 family members who were screened and were mutation negative, and 15 family members who did not undergo screening. All interviews will be audio recorded and transcribed. Transcripts will be imported into NVivo software. Interview data will be analyzed using a combined deductive and inductive approach. Questions from the interview guide will be used to develop an initial coding scheme, and inductive codes will be added as transcripts are reviewed and additional themes are noted. The first set of transcripts (N=5) will be initially independently coded by two members of the research team to develop a consensus coding scheme. Once the coding scheme is being applied consistently, one member of the research team will code the remaining transcripts. These data will be independently reviewed by two other research team members and interviews will be halted when the entire research team agree that informational redundancy has been reached. In sum, our interviews will assess how the ROR process impacted participants, how cascade screening impacted participants, why or why not participants chose to undergo screening, what were the barriers to undergoing screening, and why or why not participants followed recommendations for beta-blocker therapy.

These interviews will assess patient-reported impact of disclosure and impacts on health behaviors. They will also inform our understanding of why cascade screening of family members is or is not initiated and the extent to which cost and ease of testing (blood versus in-home saliva collection) impact screening uptake. By comparing rates of cascade screening before and after our intervention together with qualitative interviews, we can evaluate the extent to which ease, comfort, transportation issues, and cost impact the uptake cascade screening and improve our ability to apply the findings to appropriate comparable situations in clinical practice and in the most optimized manner.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

As the number of exomes and genomes sequenced grows, so does the potential for detecting clinically significant mutations in seemingly healthy individuals as secondary findings. A 'clinically significant,' or 'clinically actionable,' mutation is one for which there is a strong body of evidence that preventative action could be taken in mutation carriers to markedly reduce the risk of disease. The American College of Medical Genetics (ACMG) has identified a panel of 59 genes associated with highly penetrant genetic disorders that they consider to be clinically actionable if they harbor deleterious variants.

Recently, the Amish Complex Diseases Research Program of the University of Maryland identified a mutation (deleterious gene change) in the KCNQ1 gene, a gene known to cause Long QT Syndrome (LQTS). LQTS is associated with an increased risk of fainting (syncope) and sudden death. Beta blocker medications have been shown to reduce the risk of syncope and sudden death in LQTS by 70-90%. Therefore, identifying a mutation known to cause LQTS can lead to treatment that significantly reduces an individual's risk of serious cardiac events.

In the Old Order Amish community, the KCNQ1 variant is enriched over 100,000-fold compared to other populations. We identified 140 KCNQ1 Thr224Met carriers among our Amish Complex Disease Research cohort in whom whole exome or whole genome sequencing was performed for research purposes. These individuals were generally healthy and participated in research studies involving cardiometabolic health carried out in the Old Order Amish community of Lancaster, Pennsylvania.

With consultation from the IRB, we sent letters to these carriers describing that we had identified an apparent genetic variant that could impact their health and asked if they would like to have the genotype clinically confirmed and receive clinical evaluation. Of the 134 individuals who were mailed letters to date, 88 responded that they would like confirmation and evaluation. 16 individuals responded that they did not want to receive the results, and the remainder did not respond.

To date, 88 individuals have participated in a return of results study (ROR) for clinical confirmation of the mutation, collection of clinical information, genetic counseling, and recommendations for treatment. Genetic counseling included recommendations for all first degree relatives (who are at 50% risk of having the KCNQ1 mutation) to undergo genetic screening (cascade testing). This testing would involve going to the Clinic for Special Children and obtaining the genetic test via a blood sample for $50 per test.

Cascade testing is considered to be a highly efficient procedure for identifying additional mutation carriers who might be helped through a preventive intervention. Despite the very clear potential clinical benefit of cascade testing, uptake has traditionally been low, particularly in the United States where active screening (i.e. direct contact of relatives) is not allowed due to privacy laws.

Understanding the impact of returning these results and initiating cascade screening of family members is critical for developing best practices and optimizing the processes. Most cascade screening studies to date have been conducted outside the United States where different laws exist regarding contacting family members. Therefore, our study will attempt to address a gap in knowledge regarding whether overcoming physical and financial barriers will improve uptake of cascade screening.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Despite the very clear potential clinical benefit of screening family members of carriers to identify and counsel family members of carriers, uptake of cascade testing has traditionally been low, particularly in the United States where active screening (ie direct contact of relatives) is not allowed due to privacy laws. A study of hypertrophic cardiomyopathy found a 39% uptake of genetic counseling and testing among family members of a proband with a pathogenic mutation. Similar rates have been seen in breast cancer, and hereditary nonpolyposis colorectal cancer with update rates of 23-45%. As disease causing mutations are discovered more commonly, the investigation of the ELSI impact of this screening is paramount with greater numbers of individuals will requiring pharmacological treatment and having knowledge of their (or their children's) increased risk of sudden death. This question is particularly important with diseases with incomplete penetrance, such as LQTS. Identifying methods to increase the palatability of cascade screening within families is a high priority need.

We propose to conduct our study in the context of the Lancaster Amish, a population isolate. While there is a temptation to regard this as a limitation in terms of generalization to broader populations, this view fails to consider the magnitude of the problem in population isolates where deleterious actionable variants are most likely to be highly enriched, and frankly, where personalized medicine is most commonly practiced. We have identified 140 carriers of the KCNQ1 rs199472706 variant, and given the large family sizes of the Amish (7-8 offspring on average), this represents a huge additional pool of carriers who could potentially benefit from screening. In other words, there is a very large and disproportionate public health burden in isolate populations like the Amish (e.g., Ashkenazi, Mennonite, Hutterite, Sardinian, Icelandic, and Finnish, among others) for which population-specific screening interventions are sorely needed. As an aside, we certainly expect that lessons learned about cascade implementation in the Amish will be relevant to many other communities and populations, not just population isolates.

ID: VIEW4E02805EA0C00
Name: v2_Justification, Objective, & Research Design

HP-00081981 Supporting Literature_V2

Supporting Literature

1 * Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.***

See pages 44-50 of attached grant for summary of current literature.

2 If available, upload your applicable literature search:

Name	Created	Modified Date
Uptake of genetic testing in cardiomyopathy(0.01)	8/14/2018 2:02 PM	8/14/2018 2:02 PM
Genetic testing in channelopathies and cardiomyopathies(0.01)	8/14/2018 2:00 PM	8/14/2018 2:00 PM
ACMG 59(0.01)	8/14/2018 1:58 PM	8/14/2018 1:58 PM

ID: VIEW4E02805A7E400
Name: v2_Supporting Literature

HP-00081981 Study Procedures_V2

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

Individuals who participated in the KCNQ1 ROR study (probands) and their first degree blood-related family members will be invited to participate. All probands will be mailed an information / consent letter with a response form (uploaded in Informed Consent Section), a questionnaire about their attitudes and experience with genetic testing (uploaded to Surveys Section), and a sample family invitation letter (uploaded to Recruitment Section). In the consent letter, probands will be asked to complete and return the questionnaire as an indication that they agree to join the study. They will be informed that they may be asked to participate in an in-person interview. The letter will also ask if we can invite their adult first-degree family members who live locally to take part in the study, whether or not the proband participates. They will be given the option to enroll their minor children (with appropriate consent and assent) in the free cascade testing portion of the study. The proband will complete and return the response card to indicate whether they agree to contact of family members.

With the proband's permission, the family invitation letter will be mailed to the first-degree family members of the proband who live locally, using information from the 2009 Fisher Book and 2018 Address book of the Lancaster County Amish. At the proband's request, copies of the family invitation letter will, instead, be mailed to the proband so they can hand deliver them to family members of their choosing.

In the invitation letter, family members will be asked to take part in a study involving screening for the KCNQ1 variant, including any or all of the following: provide a saliva sample to check for the KCNQ1 genetic variant at no cost to them, complete a questionnaire about their attitudes and experience with genetic testing, and possibly take part in an in-person interview. They will be instructed to return a response form or call the Amish Research clinic if they are interested in participating in the study.

Family members who indicate, by returning the response card or by phone call, that they are interested in participating in the free genetic testing will be visited in their home by a study team member and an Amish liaison. Initial interactions are described in the Recruitment Section. For those who are interested in participating, informed consent will be obtained from adults and parents of minor children. Written assent will be obtained from minors aged 13-17; verbal assent will be obtained from children 7-12 years of age. Consent and assent will be obtained prior to any study procedures are performed. The informed consent process is detailed in the Consent Section of this application. Participants/parents will be asked to complete a questionnaire including demographics, medical and family history, and medications (uploaded in.

Sample Collection and Processing:
A saliva sample will be collected from each participant. DNA will be used for clinical testing for the KCNQ1 Thr224Met variant and an aliquot will be stored for possible future genetic analyses. Saliva samples will be collected from adults and children who are able to provide sufficient saliva volume for testing. For small children and infants, mouth swabs will be used to collect saliva.

Participants should not eat, drink, smoke or chew gum for one hour prior to collection of saliva. For saliva, participants will be asked to expectorate approximately 2 mL of saliva in an Oragene DNA (DNA Genotek, Ontario, Canada) saliva collection kit. For small children and infants, a swab will be used to collect saliva. The swab will be placed in oral cavity and sample will be collected from the right and left side of the cheek by rotating the swab 10 times in up and down motion on each side. The swab will be placed in collection container. All samples will be stored at ambient temperature until transport to the receiving laboratory.

Clinical genetic test results will be returned to the participant by a genetic counselor [MOD 6: and/or study team member. Individuals who are tested for the risk allele (positive or negative) will also be offered an electrocardiogram (ECG) along with information regarding appropriate medical follow-up, recommendations for treatment, and recommended testing of first-degree relatives.] along with information regarding appropriate medical follow-up, recommendations for treatment, and recommended testing of first-degree relatives. After they have received their KCNQ1 results, participants who agreed to take part in the survey portion will be mailed a questionnaire about their attitudes and experience with genetic testing. If the family member only agrees to completing a survey (not the KCNQ1 testing), a family information / consent letter (uploaded to Surveys Section) in the Additional documents Section) and a questionnaire will be mailed with instructions for completion and return.

Probands who indicate that they want genetic testing for their minor children who live at home will be contacted to set up an appointment for testing as described above. Minor children will not complete the survey or interview portions of the study.

Stamped and addressed envelopes will be provided for all return mailings.

A subset of participants will be asked to take part in a 1-2 hour face-to-face in-depth interview. Those who have agreed to an interview will be visited at their home by a study team member and an Amish liaison to complete the interview. The interview will be audio recorded so that it can be transcribed and analyzed.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):

N/A

3 * Describe the duration of an individual participant's participation in the study:

Study duration is dependent on which portions of the study the individual participates. Duration from receipt of the letter through the final questionnaire could span 1 1/2 years

4 * Describe the amount of time it will take to complete the entire study:

2 years

5 * Describe any additional participant requirements:

N/A

HP-00081981 Sample Size and Data Analysis_V2

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:

Our study is based on 88 KCNQ1 Thr224Met probands who were identified as part of another research study and chose to undergo clinical confirmation of their genotype and clinical evaluation for long QT syndrome. We cannot approach probands who chose not to undergo the return of results process. These 88 probands have over 700 first degree family members who may be eligible for cascade screening with our intervention. We can assume some of the family members have died and some may not live in Lancaster County, but a very large proportion will be eligible for testing. Due to privacy laws we cannot approach a family member without permission from the proband. With permission from the proband, we will send family letters or we will provide family letters to probands for them to share with family members. This study will compare the rate of uptake of cascade screening before and after our intervention of a simplified cascade screening program. Given that an individual who undergoes cascade screening before our intervention, during the 'traditional' period does not need to undergo testing again, we cannot statistically compare the difference in the proportion of family members who undergo cascade screening before and after the intervention or the statistical power that our study will have to detect a difference in uptake. That being said, our experience suggests that uptake of cascade screening will be very low among the Amish during the 'traditional' phase when cost, transportation, and an invasive test are barriers. This pilot study will test whether we can overcome these barriers and detect a meaningful improvement in uptake of cascade screening, disclosure to family members, and uptake of appropriate medical intervention. We will define this meaningful improvement a priori as a 15% improvement. For example, If we have 3% of eligible individuals undergo cascade screening during the traditional phase, we would deem 18% of eligible individuals getting tested a clinically meaningful increase. This would translate into 15/500 getting tested before our intervention and 87/485 getting tested after implementing our intervention. Another way of looking at this is that approximately 2-3 probands would initiate cascade screening before the intervention and 12-13 would after the intervention (assuming 7 children per proband).

For the interview portion of the study, participants (adults only) will be sampled purposively to include roughly 30 probands and 45 family members. In order to maximize variability with respect to the genetic test results (e.g., positive and negative), whether or not they shared their results, and primary implementation outcomes (e.g., whether or not they underwent cascade screening), we will enroll 15 probands who shared results with family members, 15 probands who did not share results, 15 family members who underwent cascade screening and were mutation positive, 15 family members who underwent cascade screening and were mutation negative, and 15 family members who did not undergo cascade screening. The goal of this sampling strategy was to achieve maximum variation and minimal informational redundancy.1 A guide for qualitative research is usually to include approximately 15 interviewees in order to obtain saturation and a homogeneous sample with maximum variation. Therefore, we expect to reach saturation and have a good representation of our participants.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

Our primary outcome is the rate of uptake of cascade screening before ('traditional') versus after ('simplified') the intervention. Uptake for this outcome is defined as the proportion of first degree family members (i.e. offspring and siblings) of the initial 88 probands who undergo cascade screening out of all eligible first degree family members (as defined by the Fisher book). We will compare the proportion before versus after the simplified screening approaches. Any individuals who undergo screening before the intervention will no longer be eligible for screening with the simplified cascade screening so the denominator will decrease accordingly. We have chosen to use the denominator of all first degree relatives defined by the Fisher book because this number is not dependent on participants returning the surveys where they will provide information on how many family members they told (and how many they have). Our secondary outcome includes the proportion of informed relatives who get screened. The number of participants screened for all outcomes will be obtained from charts (as Dr. Streeten is ordering physician for all tests).

Our secondary outcomes are:
a. Extent of disclosure of genotype results before and after the intervention. This outcome is defined as the number of family members (siblings and children) told (reported via survey) out of the total number of proband first degree relatives (known from the Fisher Book and asked on the survey).
b. Proportion of informed first-degree relatives who get screened before and after the intervention. This outcome is defined as the number of family members tested out of the number told by probands (reported via surveys)
c. The overall rate of uptake of preventative therapy among probands and family members (e.g., see a cardiologist and/or take a beta-blockers)

Analyses of secondary outcomes (a) and (b) will occur in the same manner as the primary outcome, by comparing proportions before and after the intervention. For secondary outcome (c), we don't expect the proportion of appropriately treated carriers to be impacted by our intervention, but rather the absolute number of treated individuals would be impacted by detecting more carriers with improved cascade screening. For the disclosure outcome (a), we will compare results using the denominator based on Fisher book data and based on data reported in the survey. For the uptake of screening among those informed outcome (b), the denominator is based on the survey results (the proband will be asked who they disclosed results to and the family member will be asked if their family member told them). For the uptake of clinical recommendation outcome (c), we will use data from the participants' charts to determine whether beta-blocker therapy was indicated and prescribed. We will gather data from the survey on whether participants are following the recommendations. While we don't expect our intervention to change the proportion of individuals appropriately treated, we will compare the proportions before and after the intervention to confirm this assumption.

ID: VIEW4E02806052800
Name: v2_Sample Size and Data Analysis

HP-00081981 Sharing of Results_V2

Sharing of Results

1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:

The KCNQ1 genetic testing is a clinical test and will be performed in the CLIA/CAP certified laboratory at the Clinic for Special Children. Results will be provided to participants by the genetic counselor at the Clinic for Special Children. The counselor will provide information regarding appropriate medical follow-up, treatment, and recommended testing of first-degree relatives.

An electrocardiogram will be offered to family members found to carry the risk allele. A copy of the ECG will be provided to participants.

Samples will be stored for possible future genetic analysis. These analyses are for research purposes only and results will not be shared with participants, placed in their medical records or shared with their physicians.

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

HP-00081981 Behavioral Methods and Procedures_V2

Psychological/Behavioral/Educational Methods & Procedures

You indicated on the "Type of Research" page that your study involves a psychological/behavioral/educational method or procedure such as a survey, questionnaire, interview, or focus group.

1 * Select all behavioral methods and procedures which apply to this study:

- [x] **Surveys/questionnaires**
- [x] **Key informant or semi-structured individual interviews**
- [ ] Focus groups or semi-structured group discussions
- [x] **Audio or video recording/photographing**
- [ ] Educational tests or normal educational practices (education instructional strategies, techniques, curricula, or classroom management methods)
- [ ] Individual or group behavioral observations
- [ ] Psychosocial or behavioral interventions
- [ ] Neuropsychological or psychophysiological testing
- [ ] Deception
- [ ] Other psychosocial or behavioral procedures

ID: VIEW4E09416F57800
Name: v2_Psychological/Behavioral/Educational Methods and Procedures

HP-00081981 Surveys/Questionnaires_V2

Surveys/Questionnaires

You indicated that this study involves surveys and/or questionnaires.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:
Baseline Proband questionnaire
Post-intervention Proband questionnaire
Post-intervention mutation negative Family Member questionnaire
Post-intervention mutation positive Family Member questionnaire
Family Member declined testing questionnaire
Medical, social, and family history questionnaire
Medication form

2 * Upload a copy of all questionnaires/surveys:

Name	Created	Modified Date
Family positive(0.03)	11/8/2018 1:53 PM	5/16/2022 11:33 AM
Family negative(0.03)	11/8/2018 1:51 PM	5/16/2022 11:33 AM
Family no testing(0.02)	2/3/2019 7:31 PM	5/16/2022 11:33 AM
Medication Flow Sheet.docm(0.01)	2/4/2019 12:18 PM	2/4/2019 12:18 PM
Medical, Social, and Family history form(0.01)	2/4/2019 12:17 PM	2/4/2019 12:17 PM
Proband baseline(0.03)	9/13/2018 4:06 PM	2/3/2019 7:28 PM
Proband followup(0.02)	11/8/2018 1:48 PM	2/3/2019 7:27 PM

3 * What is the total length of time that each survey is expected to take?
20 minutes

4 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)
○ Yes ● **No**

5 * Do any questions elicit information related to the potential for harm to self or others?
○ Yes ● **No**

5.1 If Yes, what procedures are in place to assure safety?

ID: VIEW4E09460F5EC00
Name: v2_Surveys/Questionnaires

HP-00081981 Interviews_V2

Interviews

You indicated that this study involves key informant or semi-structured individual interviews.

1 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

○ Yes ● **No**

2 * Upload a copy of the interview script or guide that will be used to guide the interviews:

Name	Created	Modified Date
Interview guide(0.02)	9/13/2018 4:06 PM	11/8/2018 2:02 PM

3 * What is the individual duration of each interview and what is the entire duration of the interviews?

Interviews will last approximately 1-2 hours.

4 * How will the interview responses be recorded and by whom?

The interview responses will be audio recorded with permission from the participant by the Amish Clinic nurses.

5 * Do any questions elicit information related to the potential for harm to self or others?

○ Yes ● **No**

5.1 If Yes, what procedures are in place to assure safety?

ID: VIEW4E0947A633C00
Name: v2_Interviews

HP-00081981 Audio or Video Recording_V2

Audio or Video Recording/Photographs

You indicated that this study involves audio or video recording/photographing.

1

* Indicate the type of recording (check all that apply):

- [ ] Video
- [x] **Audio**
- [ ] Still Photo
- [ ] Other

1.1

If Other, specify:

2

* What is the purpose of the recording? (i.e., for therapeutic purposes, to establish treatment fidelity, or to establish reliability of assessments)

So that the interviews can be transcribed and imported into qualitative analysis software.

3

* Could the recording be likely to cause discomfort in participants or cause harm if their confidentiality were breached?

○ Yes ● **No**

4

* How will individuals' identities be protected?

Each participant will be assigned a unique study ID. All recorded and transcribed data will be labeled with the study ID and not the participant's name. All data, along with the list that links the participant name and the study ID number will be saved on a password protected computer only accessible to the study team.

ID: VIEW4E094C128C800
Name: v2_Audio or Video Recording / Photographs

HP-00081981 Sample Collection_Analysis_V2

Sample Collection/Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

1 * What type of samples will be involved in this study? (Check all that apply)

- [x] **Prospective (will be collected)**
- [ ] Existing (previously collected at the time of initial IRB submission)

2 * Will genetic analysis/testing be done on any of the samples?

● **Yes** ○ No

3 * Will this study involve banking of samples (storing for future research use)?

● **Yes** ○ No

4 * What is the purpose of the sample collection and/or analysis?

Saliva samples will be collected for genetic testing for the KCNQ1 Met224Thr genetic variant and for storage of DNA for possible future genetic analysis.

5 * Is there the possibility that cell lines will be developed with any of the samples?

○ Yes ● **No**

6 * Will the samples be released to anyone not listed as an investigator on the protocol?

● **Yes** ○ No

6.1 If Yes, give name(s) and affiliation(s):

The Clinic for Special Children
Strasburg, PA

7 * Will the sample material be sold or given to any third parties?

○ Yes ● **No**

7.1 If Yes, give name(s) and address(es):

HP-00081981 Prospective Samples_V2

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

1 * What type of sample will be collected? (Check all that apply)

- [ ] Blood
- [ ] Bone Marrow Aspirate/Biopsy
- [ ] Cerebrospinal Fluid
- [x] **Saliva**
- [ ] Skin
- [ ] Sputum
- [ ] Stool
- [ ] Tissue
- [ ] Tumor
- [ ] Urine
- [x] **Other**

1.1 If Other, specify:
Buccal swabs

2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:

3 * What type of samples will be collected? (Check all that apply)

- [x] **Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study**
- [ ] Samples obtained specifically for research purposes-additional taken during a clinical procedure
- [ ] Leftover samples that were obtained for clinical purposes (no additional research procedures required)
- [ ] Commercial (for profit) samples
- [x] **Other**

3.1 If Other, specify:
Sample collected for research purposes will go for clinical testing and an aliquot will be banked for future research

4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?
The saliva and buccal swab samples for clinical testing will be collected in the participant's home and delivered to the CLIA-certified laboratory at the Clinic for Special Children. Samples will be labeled with participant name, DOB, date and time of collection as required by CLIA regulations for clinical samples.

An aliquot of DNA will be banked for future research analysis in order to identify possible genetic modifiers of LQTS. These samples will be labeled with a unique Study ID number.

5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):

Clinical samples sent to the Clinic for Special Children laboratory will be retained according to laboratory policy as required by federal and state regulations. If a participant withdraws from the study, samples will not be withdrawn, destroyed or anonymized.

Research samples will be destroyed if the participant withdraws consent from the study.

8 * Will the samples be destroyed after the study is over?

○ Yes ● **No**

8.1 If No, describe how the samples will be stored, where they will be stored, and for how long.

Clinical samples sent to the Clinic for Special Children laboratory will be retained according to laboratory policy as required by federal and state regulations.

Research samples will be stored indefinitely at the University of Maryland Medicine Biorepository.

ID: VIEW4E0E257D60C00
Name: v2_Prospective Samples

HP-00081981 Genetics Research_V2

Genetics Research

You indicated that genetic analysis/testing is being done on the samples.

1 * How would you classify your genetic study? (choose all that apply)

- [ ] Gene Transfer
- [x] **Pedigree Study (to discover the pattern of inheritance of a disease and to catalog the range of symptoms)**
- [ ] Positional cloning (to localize and identify specific genes)
- [ ] DNA diagnostic study (to develop techniques for determining the presence of specific DNA mutations or polymorphisms)
- [ ] Other

1.1 If Other, specify:

2 * Discuss the potential for psychological, social, and/or physical harm that could result from participation in this research. In your discussion, consider the following aspects: risks to privacy, confidentiality, insurablity, employability, immigration status, paternity status, educational opportunities, or social stigma.

1. Loss of confidentiality - In the unlikely event that confidentiality is breached, participants may experience negative emotions (e.g. anger, anxiety, embarrassment, worry). There is a risk that an unauthorized individual or entity may obtain and use a participant's health information or research results (including genetic tests) inappropriately.

2. Distress related to disclosure of genetic information - There is a chance that a participant may experience distress upon learning the results of their genetic testing

3. Discrimination - There is a risk that an unauthorized individual or entity may obtain and use a participant's genetic data inappropriately.

3 * Will subjects receive any information resulting from the genetic analysis?

(●) **Yes** ( ) No

3.1 If Yes, describe the information that subjects will receive:

Please note: genetic analysis results should only be shared if the testing will be performed in a CLIA certified lab.

Participants will receive their clinical KCNQ1 Thr224Met test results (performed in a CLIA-certified lab). Clinical genetic test results will be returned to the participant by a genetic counselor along with information regarding appropriate medical follow-up, recommendations for
treatment, and recommended testing of first-degree relatives.

4 * Will participants be offered any type of genetic or educational counseling?

(●) **Yes** ( ) No

4.1 If Yes, who will provide the education or counseling?

The genetic counselor at the Clinic for Special Children

4.2 Under what conditions will education or counseling be provided?

Participants will be instructed to go to the Clinic for Special Children for counseling on their results.

5 * Is there the possibility that a family's pedigree will be presented or published?

(●) **Yes** ( ) No

5.1 If Yes, describe how you will protect family members' confidentiality:

All identifiable information will be removed prior to publication. Furthermore, only partial pedigrees will be presented making it difficult, if not impossible to track individual subjects.

HP-00081981 Sample Banking_V2

Sample Banking

You indicated that the study involves banking of samples (storing for future research use).

1 * Where will the sample(s) be banked? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number is was approved under.)
The University of Maryland Medicine Biorepository

2 * Does the banking institution have an approved policy for the distribution of samples?
● **Yes** ○ No

3 How long will the sample(s) be kept?
Indefinitely

4 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
○ Yes ● **No**

5 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
○ Yes ● **No**

6 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
If a participant withdraws from the study, his/her remaining specimens (and materials derived from it, including DNA) will be destroyed.

7 * If the participant withdraws, explain how the data obtained from their sample(s) will be handled (e.g., will it be deleted?) ***(Please note that data for FDA regulated research cannot be deleted):***
If a participant withdraws from the study, data generated from samples prior to withdrawal may be retained and analyzed provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. Data that has been shared in public, scientific databases may not be able to be withdrawn once it has been shared.

ID: VIEW4E0E7E82B5800
Name: v2_Sample Banking

HP-00081981 Data Collection_Record_V2

Data Collection/Record Review

You indicated on the "Type of Research" page that your study involves data collection or record review (i.e., chart review, not self-report).

1 * What type of data will be collected/analyzed in this study? (Check all that apply)

- [x] **Retrospective/Secondary Analysis (data has already been collected at the time of initial IRB submission)**
- [x] **Prospective (data is not yet in existence and/or collected)**

2 * Will this study involve adding data to a registry or database for future use?

● **Yes** ○ No

3 * Will the data be released to anyone not listed as an investigator on the protocol?

● **Yes** ○ No

3.1 If Yes, give name(s) & affiliation(s):

Participant name, address, date of birth will be provided to the Clinic for Special Children laboratory with the on the clinical genetic test requisition.

ID: VIEW4E0E25A8CA400
Name: v2_Data Collection / Record Review

HP-00081981 Retrospective Data_V2

Retrospective Data

You indicated that the study involves the use of retrospective data.

1 *What is the date range that the existing data was collected?

Beginning Date:
10/12/2015
End Date:
10/31/2018

2 * What is the source of the data originally collected? (Check all that apply)

- [ ] Medical records
- [ ] Medical images
- [x] **Data collected under a different research study**
- [ ] Commercial (for profit) entity
- [ ] Publicly available records
- [ ] Other

2.1 If Other, please specify:

2.2 If you checked "Data collected under a different research study", please provide the name of study, where the study was conducted, and the IRB number (if applicable).
HP-40375 Genome Wide Research for CVD Gene-Environment Interactions
HP-40367 Genetics of Longevity in the Amish
HP-40368 Amish Family Osteoporosis Study
HP-40370 Amish Family Diabetes Study
HP-43419 Pharmacogenomics of Anti-Platelet Intervention (PAPI) Study
HP-43451 The Amish Wellness Study
HP-52685 Brain Body Connection
HP-62972 Amish Exome Sequencing: Sitosterol Study

3 * What specific data fields will you have access to/collect for the study? For example, name, initials, date of birth, Social Security number, income, demographic information, family units, housing, etc.
Probands who carry the KCNQ1 variant were identified through research testing and clinical confirmation testing performed under the above noted protocols. Their KCNQ1 variant status, name, address, and phone numbers are required to contact for study recruitment.

You can also upload a copy of the data fields/variables to be collected for the study:

Name	Created	Modified Date
There are no items to display		

ID: VIEW4E0E25AFA4000
Name: v2_Retrospective Data

HP-00081981 Prospective Data_V2

Prospective Data

You indicated that the study involves the collection of prospective data.

1 * Where is the data being collected from? (Check all that apply)

- [ ] Medical records
- [ ] Medical images
- [ ] Commercial (for profit) entity
- [ ] Publicly available records
- [ ] Schools
- [x] **Other**

1.1 If Other, please specify:
Participant report

2 * What data fields will you have access to/collect for the study? For example, name, initials, date of birth, Social Security number, income, demographic information, family units, housing, etc.
Data includes name, address, phone number date of birth, gender, ethnicity, race, medical and family history, medications and study assessments (questionnaire and interview responses) listed in the procedure section of this application.

You can also upload a copy of the data fields/variables to be collected for the study:

Name	Created	Modified Date
There are no items to display		

HP-00081981 Data Registry_V2

Data Registry

You indicated that the study involves adding data to a registry or database for future use.

1 * What is the name of the registry/database to which data will be added? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number it was approved under.)

1. UM Amish Index Database
2. OASIS
3. Possible other large NIH databases (e.g. Database of Genotypes & Phenotypes (dbGaP), ClinVar)

2 * What is the purpose of the registry/database?

1. The Amish Index Database is a relational database that contains a record of all individuals who have participated in research studies at the Amish Research Clinic in Lancaster PA under the direction of Drs. Alan Shuldiner and Braxton Mitchell. The database includes participant's name, date of birth, address, Fisher number, Fisher relationship, Subject ID numbers for each Amish study protocol that the individual has been enrolled in, and their NIH Anabaptist Genealogy Database (AGDB) number with related information to construct pedigrees. As part of the IRB-approved protocols, Amish research participants may provide consent to be recontacted for the opportunity to participate in future studies. The database is used to maintain current contact information for mailing out Amish Research Clinic newsletters and offering participants opportunities to participate in future studies and to construct pedigrees that are necessary for the genetic analyses associated with the research. The database is linked to study-specific genotype and phenotype data that can be used for primary and secondary analyses consistent with IRB approved consents.

2. OASIS (-Omics Analysis, Search, and Information System) is a searchable database that includes genetic association results and is accessible by members of the Amish research group and their approved collaborators. Genetic analyses are pre-computed and the association results are loaded into the database. The database also contains limited amounts of individuals level access to allow drawing of pedigrees and more detailed genetic results. However, users are never able to see individual level results.

3. Large public databases, for example: The database of Genotypes and Phenotypes (dbGaP) archives and distributes the results of studies that have investigated the interaction of genotype and phenotype. Such studies include genome-wide association studies, medical sequencing, molecular diagnostic assays, as well as association between genotype and non-clinical traits.

ClinVar is an NIH/NCBI-supported database containing medically relevant variants and their clinical interpretations. ClinVar supports the medical genetics community as a freely available, public archive of the relationships between medically important variants and phenotypes. It allows testing laboratories access to a broader set of clinical interpretations than they may have collected on their own, and the ClinVar data can be incorporated into their daily workflow. Data submitted includes variant description (either HGVS or genomic location and change) and a clinical assertion and/or phenotype. Other supporting evidence may be submitted including such as the number of observations of the variant, allele frequency, co-segregations, and mode of inheritance for variant level data. For case-level data, submission of affected status, presence of family history, bi-allelic variant occurrence, and ethnicity are encouraged to support review.

3 * Who has oversight and controls access to the registry/database?

1. Dr. Mitchell and designated data managers have access to the Amish Index Database and phenotype and genotype databases.
2. Dr. James Perry administers access to OASIS. To be granted access, investigators must sign a confidentiality attesting that they will keep analysis results confidential. Users are unable to see any individual level data in OASIS.
3. dbGaP provides two levels of access - open and controlled. Summaries of studies and the contents of measured variables as well as original study document text are generally available to the public, while access to individual-level data including phenotypic data tables and genotypes require varying levels of authorization. Controlled-access data can only be obtained if a user has been authorized by the appropriate Data Access Committee (DAC).

4 * Who will have access to the registry/database?

1. Dr. Mitchell and designated data managers have access to the Amish Index Database and phenotype and genotype databases.
2. Dr. James Perry administers access to OASIS. To be granted access, investigators must sign a confidentiality attesting that they will keep analysis results confidential. Users are unable to see any individual level data in OASIS.
3. dbGaP provides two levels of access - open and controlled. Summaries of studies and the contents of measured variables as well as original study document text are generally available to the public, while access to individual-level data including phenotypic data tables and genotypes require varying levels of authorization. Controlled-access data can only be obtained if a user has been authorized by the appropriate Data Access Committee (DAC).

5 * How long will the data be stored in the registry/database?

Indefinitely

6 * Are participants in the study allowed to request that their data be removed?

◯ Yes ● **No**

6.1 If No, explain why subjects will not be able to request that their data be removed:

If a study participant withdraws consent, the data in the Amish Index Database will be retained identified only by study ID or Amish Index ID number. The data in these databases have been used to support numerous analyses and must be maintained to ensure data is verifiable.

The policies of the NCBI ClinVar database do not allow removal of data submissions. Case level data is not identifiable. The NIH GWAS data repository (dbGAP) has developed policies with regard to removal of individual data records if consent is withdrawn. Submitting investigators and their institutions may request removal of data on individual participants from the data repository in the event that a research participant withdraws consent. However, data that have already been distributed for approved research use will not be able to be retrieved.

ID: VIEW4E0E25BCFA400
Name: v2_Data Registry

HP-00081981 Clinical Trial Registration_V2

Clinical Trial Registration

You indicated on the "Type of Research" page that your study is a clinical trial.

1 * Does the UM Clinical Trials Registry policy require registration of this trial?
● **Yes** ○ No

2 * Has this trial been registered?
● **Yes** ○ No

ID: VIEW4E093BF078C00
Name: v2_Clinical Trial Registration

HP-00081981 Clinical Trial Registration Info_V2

Clinical Trial Registration Information

You indicated that this clinical trial has been registered.

1 * Was this trial registered at www.clinicaltrials.gov?
(●) **Yes** ( ) No

2 If no, was this trial registered on a site other than clinicaltrials.gov?
( ) Yes ( ) No

2.1 If Yes, specify the name of the other site:

2.2 Provide justification for registering this trial on this site:

3 * Registration Number
NCT03783975

ID: VIEW4E093BF1D0800
Name: v2_Clinical Trial Registration Information

HP-00081981 Participant Selection_V2

Participant Selection

1 * How many local potential participants (or specimens/charts) do you anticipate will be screened for this study? ***Screening includes determining potential participants' initial eligibility for and/or interest in a study.***
700

2 * How many participants (or specimens, or charts) will be enrolled/used for this study? ***A local prospective participant is considered enrolled in the study when a UM-approved Informed Consent Document (not including separate screening consent forms) is signed.***

Local - the number being enrolled at this site:
500

Worldwide - the number being enrolled total at all sites (including local enrollment):
500

3 * Gender:

- [x] **Male**
- [x] **Female**

4 * Age(s):

- [x] **0 to 27 days (newborn infants)**
- [x] **28 days to 12 months (Infant)**
- [x] **13 months to 23 months (Toddler)**
- [x] **2 to 5 years (Preschool)**
- [x] **6 to 11 years (Child)**
- [x] **12 to 17 (Adolescents)**
- [x] **18 to 88 years (Adult)**
- [x] **89 years and older**

5 * Race/Ethnicity:

- [ ] All Races Included
- [ ] American Indian or Alaskan Native
- [ ] Asian/Other Asian
- [ ] Asian/Vietnamese
- [ ] Black or African American
- [ ] Hispanic or Latino
- [ ] Mixed Race or Ethnicity
- [ ] Native Hawaiian or Pacific Islander
- [x] **White or Caucasian**

6

* Language(s):

- [x] **English**
- [ ] Chinese

- [ ] French
- [ ] Italian
- [ ] Japanese
- [ ] Korean
- [ ] Local Dialect
- [ ] Spanish
- [ ] Vietnamese
- [ ] Other

6.1 Specify Other:

7

* Are you excluding a specific population, sub-group, or class?

◯ Yes ● **No**

7.1

If Yes, indicate your justification for excluding a specific population, sub-group, class, etc.:

HP-00081981 Vulnerable Populations_V2

Vulnerable Populations

1 * Will you be targeting ANY of the following Vulnerable Populations for enrollment? (Select all that apply)

- [x] **Employees or Lab Personnel**
- [x] **Children (Minors)**
- [ ] Cognitively Impaired/ Impaired Decision Making Capacity
- [x] **Pregnant Women/Fetuses**
- [ ] Wards of the State
- [ ] Students
- [ ] Prisoners
- [ ] Nonviable Neonates or Neonates of Uncertain Viability
- [ ] Economically/Educationally Disadvantaged
- [ ] None of the above

Only select populations which you will be targeting for enrollment. Do not include populations that may be enrolled incidentally. Enrollment of a vulnerable population is considered to be "targeted" if the study team will be aware that a subject is from a vulnerable group as a result of interaction with the subject or collection of specific information about the subject, and the research team does not wish to exclude them. "Incidental" enrollment is limited to situations where a study team is unaware that a subject is from a vulnerable group.

ID: VIEW4E0E519917800
Name: v2_Vulnerable Populations

HP-00081981 Vulnerable Populations Employees_V2

Vulnerable Populations - Employees or Lab Personnel

You indicated that employees or lab personnel are included in this study.

1 * Describe how you will ensure particiption in this research will not affect employment and prevent undue influence:

Employees and Lab Personnel are not targeted for enrollment, however, there are some members of the Amish community who are employed as liaisons at the Amish Research Clinic and therefore may be eligible for participation. Informed consent will be obtained in the same way as obtained by other volunteers. Potential participants will be informed during the informed consent process that if a person is an employee or student, their employment status or academic standing at UMB will not be affected by participation, non-participation or withdrawal from the study and that they may leave the study without penalty or loss of benefits to which he/she is normally entitled from the University of Maryland or its affiliated institutions. Privacy and confidentiality will be protected as described in the appropriate sections of this application.

ID: VIEW4E0E5192BA800
Name: v2_Vulnerable Populations - Employees or Lab Personnel

HP-00081981 Vulnerable Populations Children_V2

Vulnerable Populations - Children

You indicated that children are included in this study.

1 * Describe how you will prevent undue influence:

This project will be open to patients including those <18 years of age. Permission for a minor to be enrolled in the research study will be obtained from a parent or legal guardian of the child. Parental permission will be documented by signing the consent form. In addition to permission of the parent(s) or guardian, written assent to participate in the study will be obtained from minors 13-17 years of age. After explaining the study verbally to both the parent(s) and adolescent, they will be asked to read the forms and sign the consent and assent forms.

Children younger than 13 years will have key points of the study explained in language understandable and appropriate to their developmental level and verbal assent will be obtained. For very young children (<7 years of age) and infants we will not obtain assent, but will not include any patient who does not cooperate or seem unwilling to comply with the procedures.

At least one parent will be asked to sign the Consent form for all potential participants under the age of 18. If the parent provides consent for his/her child, but the child does not wish to participate, the child will not be enrolled in the study. If the parent refuses participation of their child, then the child will not be enrolled regardless of the child's wishes. Participants will be given a copy of their signed consent form, which will contain the contact information for the research team.

Parents and children will be given the opportunity to ask questions at all times during the assent/consent procedure and study. We will attempt to contact and re-consent participants who were enrolled as minors when they turn 18 years of age. If we are unable to contact the participant, or if the participant declines to consent, the participant will be withdrawn from the research at that time.

1.1

* Choose the risk level(s) that to your research:

- (●) **45 CFR 46.404/21 CFR 50.51 - The research presents no greater than minimal risk to the children.**
- ( ) 45 CFR 46.405/21 CFR 50.52 – The research presents greater than minimal risk but presents the prospect of direct benefit to the individual participants.
- ( ) 45 CFR 46.406/21 CFR 50.53 - The research presents greater than minimal risk and no prospect of direct benefit to the individual participants, but likely to yield generalizable knowledge about the participant's disorder or condition. ***Please note that Institutional Official approval is also required.***
- ( ) 45 CFR 46.407/21 CFR 50.54 – Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. ***Please note that Institutional Official approval is also required.***

Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.

1.2 * Provide justification for the risk level selected above:

The risk for children to participate in the study is minimal. Loss of confidentiality and collection of a buccal swab or saliva sample represent no greater risk than what may be encountered in everyday life.

ID: VIEW4E207F69EE800
Name: v2_Vulnerable Populations - Children

Vulnerable Populations - Pregnant Women/Fetuses

You indicated that pregnant women are included in this study.

1 * Describe how you will prevent undue influence:
We are not targeting pregnant women for enrollment into the study, however, if they are first degree relatives of participant carriers of the KCNQ1 mutation they may be offered enrollment in the same manner as other first degree relatives. Informed consent will be obtained in the same manner as with other volunteers. No exculpatory language will be used in the consent process. It will be stressed the participation is voluntary and refusal to participant will not result in loss of benefits otherwise due. All questions will be answered to the individuals satisfaction before deciding whether or not to enroll.

2

* What risk to subjects is presented by this research? ***If the research does not fall under one of the categories below, it will require submission to OHRP prior to any IRB approval. Please consult the HRPO staff for further guidance.***

- ○ Greater than minimal risk with prospect of direct benefit ONLY to fetus
- ○ Greater than minimal risk with prospect of direct benefit to pregnant woman only OR to both pregnant woman and fetus
- ○ Minimal risk to pregnant woman and fetus without the prospect of direct benefit, but the research proposes the development of important biomedical knowledge which cannot be obtained by any other means
- ● **Minimal risk with prospect of direct benefit to pregnant woman only OR to both pregnant woman and fetus**
- ○ Minimal risk with prospect of direct benefit ONLY to fetus
- ○ None of the Above

Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.

3 * If scientifically appropriate, provide information about preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, that have been conducted and provide data for assessing potential risks to pregnant women and fetuses: (i*f not scientifically appropriate, enter "N/A".*)
N/A

4 * Explain why the identified risks are the least possible for achieving the objectives of the research:
The risks associated with obtaining a saliva-based sample does not represent an increase over the risk associated with routine medical examinations of pregnant

women. As no further active interventions will be performed, there are no risks or benefits to the fetus.

5 * Explain how each individual providing consent will be fully informed and kept fully informed regarding the reasonably foreseeable impact of the research on the fetus:
There is no foreseeable impact of the research on the fetus.

6 * Will inducements, monetary or otherwise, be offered to terminate a pregnancy?
○ Yes ● **No**

7 * Will individuals engaged in the research have any part in any decisions as to the timing, method, or procedures used to terminate a pregnancy?
○ Yes ● **No**

8 * Will individuals engaged in the research have any part in determining the viability of a neonate?
○ Yes ● **No**

ID: VIEW4E0E5195C0000
Name: v2_Vulnerable Populations - Pregnant Women / Fetuses

HP-00081981 Eligibility_V2

Eligibility

1 * Do you have an existing Eligibility checklist(s) for this study?

◯ Yes ● **No**

1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE**. The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date

There are no items to display

1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	KCNQ1 Thr224Met proband or first degree family member of KCNQ1 Thr224Met carrier

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

	Number	Criteria
View	1	Family members who the proband has not provided permission to discuss the study with.

After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.

Eligibility Checklist for HP-00081981_5 v12-17-2019-1576614234540(0.01)

ID: VIEW4E0E5185F9000
Name: v2_Eligibility

HP-00081981 Recruitment_V2

Recruitment

1 * Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):

Individuals who participated in the KCNQ1 ROR study (probands) and their first degree blood-related family members will be invited to participate. First degree family members of identified carriers will also be eligible for testing.

All probands who underwent the return of results process (n=88 to date) will be mailed an information / consent letter and response form (uploaded in Informed Consent Section), a questionnaire about their attitudes and experience with genetic testing (uploaded to Surveys Section), and a sample family invitation letter (uploaded below). These participants all agreed to recontact during the consent process for the study their KCNQ1 ROR was conducted under (see Retrospective Data Section). In the information/consent letter, probands will be asked to complete and return the questionnaire as an indication that they agree to join the study. They will be informed that they may be asked to participate in an in-person interview. The letter will also ask if we can invite their adult first-degree family members who live locally to take part in the study, whether or not the proband participates. They will be given the option to enroll their minor children (with appropriate consent and assent) in the free cascade testing portion of the study. The proband will complete and return the response form to indicate whether they agree to contact of family members.

With the proband's permission, the family invitation letter will be mailed to the first-degree family members of the proband using information from the 2009 Fisher Book and 2018 Address book of the Lancaster County Amish. At the proband's request, copies of the family invitation letter will, instead, be mailed to the proband so they can hand deliver them to family members of their choosing. The family invitation letter will explain our intervention offering free, mail-in, saliva testing of first degree family members.

2 * Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study, enter "N/A"):

During in person visits with family member, it will be made clear that participation in the study is voluntary and should not be influenced by participation or lack of participation of other family members. All questions will be answered. Open questions will be asked to confirm that the subject understands the study protocol. The Amish liaison will be available to explain or interpret as needed. They will be given ample time to consider participation. They will be reminded during the consent process that the study is voluntary and there will be no penalty or loss of benefits if they choose not to participate.

3 * Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)

- [x] **PI**
- [x] **Study Staff**
- [ ] Third Party

3.1 If you are using a third party, specify Third Party Recruiters:

4 Upload any recruitment tools such as screening/telephone scripts and introductory letters (do not upload advertisements here):

Name	Created	Modified Date
Proband invitation letter(0.02)	3/4/2019 11:58 AM	1/5/2020 1:58 PM
Family letter(0.02)	11/8/2018 2:13 PM	2/3/2019 7:34 PM

ID: VIEW4E0BCAA0A6C00
Name: v2_Recruitment

HP-00081981 Advertising_V2

Advertising

1 * Will you be using advertisements to recruit potential participants?

◯ Yes ● **No**

ID: VIEW4E0BCCF811000
Name: v2_Advertising

HP-00081981 Research Related Risk_V2

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

1 * Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:

Family Members:

1. There are no known risks associated with providing a saliva sample or buccal swab.
2. Distress related to disclosure of genetic information - There is a risk that a participant may experience emotional distress upon learning that they or a family member have a genetic variant associated with Long QT Syndrome. To minimize this risk, clinical genetic test results will be returned to the participant by a genetic counselor along with information regarding appropriate medical follow-up, recommendations for treatment, and recommended testing of first-degree relatives.
3. Discrimination - There is a risk that an unauthorized individual or entity may obtain and use a participant's genetic data inappropriately. The diagnosis of Long QT syndrome or documentation of carrying the KCNQ1 genetic variant could be stigmatizing and could be used to make it harder for an individuals to get or keep a job, life or other insurances. There are laws against using genetic information in this way but they may not give full protection for life, long-term care, or disability insurances.
4. Loss of confidentiality - In the unlikely event that confidentiality is breached, participants may experience negative emotions (e.g. anger, anxiety, embarrassment, worry). There is a risk that an unauthorized individual or entity may obtain and use a participant's health information or research results (including genetic tests) inappropriately. To minimize the risk of loss of confidentiality, study files containing identifying information (e.g. consent form, contact information) will be stored in a secure location such as a locked office or locked cabinet. Participants will be assigned a unique Study ID number which will be used to identify research samples and data. Data will be stored in a controlled-access, database. Access to the study identification codes or other personally identifiable information will be restricted to the PI, essential study team members and, upon written request, to the IRB or other appropriate regulatory agencies. Confidentiality will be preserved to the fullest extent possible by the research team.
5. Genetic research: Genetic material from samples will be stored securely and may be used for future genetic research following IRB approval. Results will not be communicated to participants, their healthcare providers or placed in medical records. Since we will not be returning individual research results to participants, we believe the risk that a participant would experience psychological or social harm from knowledge about medical condition is very low. There is a risk that an unauthorized individual or entity may obtain and use a participant's research data (including genetic tests) inappropriately. The Genetic Information Nondiscrimination Act (GINA) provides some protection against discrimination from health insurance and employers based on genetic information, however it does not protect against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.
6. Data Sharing in Public Databases: There is a risk that the information in a scientific database can be traced back to a study participant, since even without any identifying information, genetic information is unique to each individual. We believe the chance of this happening is very small.
7. There are no known risks associated with obtaining an electrocardiogram.

Probands will complete questionnaires and interviews only therefore only risk of loss of confidentiality noted above applies to probands.

ID: VIEW4E1B52509F000
Name: v2_Research Related Risks

HP-00081981 Potential Benefits_V2

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the potential direct benefit(s) to participants:
Participants may benefit by being diagnosed with LQTS and being able to take preventative steps to reduce the risk of sudden death.

2 * Describe the importance of the knowledge expected to result from the study:
The knowledge gained from this study is important because of the recent growth of availability of whole genome sequence data and our need to address the challenge of how best to address secondary findings from these data. This study provides the opportunity to evaluate strategies for returning genetic results to individuals discovered to have actionable variants and enhanced screening of their family members.

3 * Describe how the potential risks to participants are reasonable in relationship to the potential benefits:
The potential benefit of this study is to learn how to improve screening rates of family members of individuals with an actionable pathogenic variant and to understand what the impact of testing is on participants. This benefit outweighs the minimal risks possible associated with the research.

4 * Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects.
The alternative to participating in the study is to get genetic testing for the KCNQ1 mutation on their own.

ID: VIEW4E1B5251B0400
Name: v2_Potential Benefits and Alternatives

HP-00081981 Withdrawal of Participants_V2

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/A".

1 * Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:
Participants may be withdrawn from the research without their agreement if funding is discontinued.

2 * Describe procedures for orderly termination:
This is not a treatment study, therefore there are no measures that need to be taken to protect a participants safety. If a participant withdraws participation, no further testing will be performed on samples collected. All data collected will be used for the research and analysis described in this protocol.

3 * Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:
Upon request of a participant to withdraw from the study, we will cease data collection. Participants who have had KCNQ1 clinical testing performed will be informed of test results if they withdraw prior to results disclosure and they still wish to receive result notification. Data generated from samples and health information collected prior to withdrawal may be retained and analyzed provided such analysis falls within the scope of the analysis described in the IRB-approved protocols. Data that has been shared in public, scientific databases will not be withdrawn once it has been shared.

ID: VIEW4E1B52531F800
Name: v2_Withdrawal of Participants

HP-00081981 Privacy of Participants_V2

Privacy of Participants

If the study does not involve interaction with participants, answer "N/A" to the questions below.

1 * Describe how you will ensure the privacy of potential participants throughout the study ***(privacy refers to persons and their interest in controlling access to themselves):***

Participant interactions will take place in the privacy of the participant's home at a time the participant feels comfortable and agrees to talk. Participants may elect to have a family member or significant other present during research interactions. The participant is in control of who is present and can choose to postpone discussion until a later time if they choose.

2 * Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:

The consent process, survey completion, specimen collection and interviews will be performed in the privacy of the participant's home. Typically these interactions occur in the kitchen or living room. Not uncommonly small children are present when the consent is performed. Interactions in the kitchen or living room is the culturally accepted setting for these types of interactions. It would be inappropriate to use other more private settings in the home, i.e., the bedroom, for these interactions.

3 * Describe potential environmental stressors that may be associated with the research:

Potential stressors include if some family members wish to participate and others do not. We will endeavor to ensure that no family member feels coerced into participating just because another family member is participating by obtaining individual consent from each participant and stressing that this is strictly voluntary and no one is required to participate.

4 * Will this study have a site based in the European Union?

◯ Yes ● **No**

5 * Will the study have planned recruitment or data collection from participants while they are located in the European Union?

◯ Yes ● **No**

Access link below for information about the EU General Data Protection Regulations to assist in answering these questions.
https://www.umaryland.edu/oac/general-data-protection-regulation/

ID: VIEW4E1B525B87C00
Name: v2_Privacy of Participants

HP-00081981 Confidentiality of Data_V2

Confidentiality of Data

1 * Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?

- (●) **Yes**
- ( ) No, the data will be stored de-identified/anonymous (stripped of all identifiers, no way to identify individual participants)

2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)

All research data will be stored in password protected, controlled-access databases. Individual subject research records with identifiers (eg. consent forms, HIPAA authorizations and lab results) will be stored in locked cabinets in the locked offices of designated research staff.

3 * How will such data be secured?

All electronic data will be stored in a password protected, controlled-access study database. Paper records will be stored in locked file cabinets within locked offices.

4 * Who will have access to research data?

The Principal Investigator and designated research team members. Access will be restricted to the extent needed to fulfill the role individual team member are assigned.

5 * Will study data or test results be recorded in the participant's medical records?

( ) Yes (●) **No**

6 * Will any data be destroyed? ***(Please note that data for FDA regulated research and VA research cannot be deleted)***

( ) Yes (●) **No**

6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?

7 Do you plan to obtain a Certificate of Confidentiality?

( ) Yes (●) **No**

7.1 If Yes, upload your Certificate of Confidentiality. If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document.

Name	Created	Modified Date
There are no items to display		

8 * Discuss any other potential confidentiality issues related to this study:

None

ID: VIEW4E1B5265E0400
Name: v2_Confidentiality of Data

HP-00081981 Monitoring Plan Selection_V2

Monitoring Plan Selection

1 * Type of data safety monitoring plan for the study:

- ○ Will use/defer to the external sponsor's Data Safety Monitoring Plan
- ○ Data Safety Monitoring by a Committee
- ● **Data Safety Monitoring by an Individual**
- ○ There is no data safety monitoring plan in place

ID: VIEW4E1B00E30D400
Name: v2_Monitoring Plan Selection

HP-00081981 Monitoring Plan - Individual_V2

Monitoring Plan - Individual

You indicated that the monitoring will be done by an Individual.

1 * Identify the individual who will be performing the safety monitoring:
Amber Beitelshees

2 * Describe this individual's role in relation to the protocol:
Principal Investigator

3 * What data will be reviewed?

- [x] **Adverse Events**
- [x] **Enrollment Numbers**
- [ ] Patient Charts/Clinical Summaries
- [x] **Laboratory Tests**
- [ ] Medical Compliance
- [ ] Procedure Reports
- [ ] Raw Data
- [x] **Outcomes (Primary, Secondary)**
- [ ] Preliminary Analyses
- [ ] Other

3.1 If Other, specify:

4 * What will be the frequency of the review?

- (●) **Annually**
- ( ) Bi-Annually
- ( ) Other

4.1 If Other, specify:

5 * Safety monitoring results will be reported to:

- [x] **IRB**
- [ ] GCRC
- [ ] Sponsor
- [ ] Other

5.1 If Other, specify:

ID: VIEW4E1B026A2A400
Name: v2_Monitoring Plan - Individual

HP-00081981 Research Related Costs_V2

Research-Related Costs

1 * Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?

- ○ No
- ● **Yes**

1.1 If Yes, check all that apply:

- ☑ **Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)**
- ☐ Investigational or Study Device
- ☐ Investigational or Study Drug
- ☐ Investigational Procedure(s)

1.2 If No, who is responsible for payment?

2 * Who is responsible for the uncovered research-related costs?

- ☐ Participant
- ☐ Sponsor
- ☐ UM
- ☐ Other
- ☑ **There will be no uncovered research-related costs**

2.1 If Other, specify:

3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:

HP-00081981 Compensation for Research Related Injury_V2

Compensation for Research-Related Injury

1 * Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?

◯ Yes ● **No**

1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date
There are no items to display		

1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?

◯ Yes ● **No**

1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

1.2.2

Name	Created	Modified Date
There are no items to display		

ID: VIEW4E1B629EEC000
Name: v2_Compensation for Research-Related Injury

HP-00081981 Payment to Participants_V2

Payment/Reimbursement to Participants

1 * Will participants receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research?

(●) **Yes** ( ) No

ID: VIEW4E1C52A5D7800
Name: v2_Payment to Participants

HP-00081981 Payment Detail_V2

Payment/Reimbursement Detail

You indicated that participants will receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research.

1 * Payment/reimbursement to participants will be for: (check all that apply)

- [ ] Travel
- [ ] Parking
- [ ] Meals
- [ ] Lodging
- [x] **Time and effort**
- [ ] Other

1.1 If Other, specify:

2 * What is the total dollar value of the payments/reimbursements over the duration of the study? ***Total payment(s) for participation in research of $600 or more in a calendar year is required to be reported on an IRS Form 1099.***

up to $85

3 * Describe the timing and distribution plan for the payment/reimbursement (schedule, means, etc.)?

Probands will be compensated up to $85 over the course of the study. Five dollars in cash will be included in each of the two mailed surveys. If a proband participates in an interview, a check in the amount of $75 will be mailed to them 6-8 weeks after the interview.

Family members will be compensated up to $85. If a family member participates in an interview, a check in the amount of $75 will be mailed to them 6-8 weeks after the interview.

Mod 14 - Participants who complete and return the mailed questionnaire will have the option to choose from a listing of 2-3 community-based 501c3 charities to receive a $5 cash donation as compensation for completing the questionnaire.

4 * Method(s) of payment/reimbursement to be Used:

- [x] **Cash**
- [x] **Check**
- [ ] Money Order
- [ ] Gift Certificate/Gift Card
- [ ] Other

4.1 If Other, specify:

HP-00081981 HIPAA_V2

HIPAA (Health Insurance Portability and Accountability Act)

1 * Are you affiliated with, or will you be accessing data from a HIPAA-covered entity? A covered entity might be a hospital, a physician practice, or any other provider who transmits health information in electronic form.

• At UMB, this includes UMB schools designated as covered entities (School of Medicine and School of Dentistry) and entities under the University of Maryland Medical System (UMMS). The Baltimore VA Medical Center is also a covered entity.

• If you are a researcher from any school that is not a covered entity but is accessing electronic medical records from a covered entity (such as UMMC), HIPAA would be applicable. Please see a list of covered entities included under UMMS here: *executed-ace-designation-042018.pdf*

● **Yes** ○ No

2 * If Yes, will the study view, access, share, collect, use, or analyze health information that is individually identifiable under HIPAA?

● **Yes** ○ No

ID: VIEW4E1B0A2114400
Name: v2_HIPAA

HP-00081981 Protected Health Information_V2

Protected Health Information (PHI)

You indicated that HIPAA applies and the study will view, access, share, collect, use, or analyze health information that is individually identifiable.

1 * Which PHI elements will be used or disclosed in this study? (Check all that apply)

- [x] **Name**
- [x] **Address (if more specific than Zip Code)**
- [x] **Dates**
- [x] **Ages over age 89**
- [x] **Telephone numbers**
- [ ] Fax numbers
- [ ] Email addresses
- [ ] Social Security numbers
- [ ] Medical record numbers
- [ ] Health plan beneficiary numbers
- [ ] Account numbers
- [ ] Certificate/license numbers
- [ ] Vehicle identifiers and serial numbers, including license plate numbers
- [ ] Device identifiers and serial numbers
- [ ] Web universal resource locators (URLs)
- [ ] Internet protocol (IP) address numbers
- [ ] Biometric identifiers, including fingerprints and voiceprints
- [ ] Full-face photographic images and any comparable images
- [x] **Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification**
- [ ] None

2 * Why is the PHI necessary for this research?
If SSNs are going to be used, describe the specific use and type of SSN to be used (real, scrambled, last 4 digits).
The above noted identifiers are needed to contact participants to offer participation and communicate with participants during the course of study participation; to establish a link between the unique study id and the individual ; and social security numbers are required to obtain participant compensation

3 * What is the source(s) of the PHI?
Participant and the Fisher Book and Church directory of the Old Order Amish of Lancaster County.

4 * Provide written assurance that Protected Health Information will not be reused. (Note: this refers to re-use on another study or for a purpose which has not been approved, not to the re-use of screening data during the current study).
The PHI collected from participants will only be used for the uses approved in this protocol. Only subjects who agree to recontact for future studies (see consent form) may be approached to offer participation in other studies.

5 * How will permission to allow the use/disclosure of the individual's protected health information (PHI) be obtained? (Choose all that apply:)

- [x] **Obtain written authorization *(upload authorization form at the end of the application under "Consent and HIPAA Authorization Forms")***
- [x] **Requesting waiver/alteration of authorization (includes waiver of authorization for recruitment only)**
- [ ] Qualifies as a limited data set (LDS)

5.1 If you are using a limited data set (LDS), please attach the Data Use Agreement (DUA):

Name	Created	Modified Date

There are no items to display

ID: VIEW4E1B0A24AA400
Name: v2_Protected Health Information

HP-00081981 Waiver - Alteration of Authorization_V2

Waiver/Alteration of Authorization

You indicated that a waiver/alteration of authorization is requested.

1 * Provide rationale for how the research presents no more than minimal risk to the privacy of individuals:
We are requesting a waiver of authorization for the survey portion of this research. Completion of the survey, if the individual chooses to do so, represents similar risk to privacy to that which would be encountered in everyday life, for instance, in the context of standard medical care. Moreover, the participant can choose not to respond without any penalty or loss of benefit otherwise entitled.

2 * Describe the plan to ensure the protection of PHI collected during this study from improper use and disclosure:
All returned surveys will be secured in locked cabinets or locked offices of the study data manager upon receipt. Survey data will be entered in password-protected, secure databases behind the UMSOM firewall. Computers are password protected and located in secure offices. Access to the paper and electronic information is only given to research team members for whom it is essential to their study role or responsibilities.

3 * Describe the plan to destroy the PHI collected during this study at the earliest opportunity consistent with the conduct of the research. If there is a need to retain PHI, provide a justification:
We will not destroy the PHI collected with the returned questionnaires. We need to retain the family relationship information of the participants completing surveys.

4 * Why could the research not practicably be done without access to and use of this PHI?
We could not identify and mail questionnaires to participants without access to and use of this PHI.

5 * Why could the research not practicably be done without the waiver or alteration?
Because the documentation of consent has been waived it would not be practical to include a HIPAA authorization.

6 * Will the subjects' PHI be disclosed to (or shared with) any individuals or entities outside of UM?
○ Yes ● **No**

6.1 If Yes, describe the individuals or entities outside of UM to whom PHI will be disclosed.

ID: VIEW4E1B0A2896400
Name: v2_Waiver/Alteration of Authorization

HP-00081981 Informed Consent Process_V2

Informed Consent Process

If the study does not involve interaction with participants or a waiver of consent is being requested , answer "N/A" to the questions below.

1 * Indicate the type(s) of consent that will be involved in this study: (check all that apply)

- [ ] Not applicable (study may qualify as exempt)
- [ ] Request to Waive Consent/Parental Permission (Consent is not being obtained)
- [ ] Request to Alter Consent (Some Elements of Consent Waived)
- [x] **Request to Waive Documentation of Consent (Verbal/Oral Consent)**
- [x] **Written Consent Form**
- [ ] Electronic Consent

2 * Describe the Informed Consent process in detail:

Family member consent process: Family members will be visited in their home after the ARC staff receives their response card expressing interest in testing, or possibly if no response is received. Participants will be approached by a study team member (usually a nurse) and an Amish liaison. The study will be briefly explained to the participant who will be asked if they would like to hear more about the study for possible participation. If they are unsure, information will be given with the name and phone # of the study team member to contact if they are interested in hearing more in the future. If the potential participant expresses interest in the study and invites the study team into their home, the study will be explained in detail using the consent form. The potential participant will be invited to ask questions throughout the process and will be reminded often that the study is voluntary. Ample time will be given to make a decision regarding participation in the study. If they decide to participate the consent form will be signed and dated by both the participant and the study team member.

We are requesting a Waiver of Documentation of Consent for probands and family members who decline genetic testing. These individuals will be mailed an information / consent letter along with a questionnaire.

3 * Confirm that the consent process will explain the following:

- The activities involve research.
- The procedures to be performed.
- That participation is voluntary.
- The name and contact information for the investigator.

(●) **Yes** ( ) No

4 * Describe who will obtain Informed Consent:

Designated, trained members of the research team will obtain informed consent.

5 * If obtaining consent from a legally authorized representative (LAR), describe how you will confirm that the individual is the LAR and can provide legally effective informed consent. *(Answer "N/A" if not obtaining consent from LARs)*

N/A

6 * Describe the setting for consent:

Consent obtained in the home is done in private whenever possible. If young children are present and the research volunteer is their caregiver, it is sometimes not feasible to separate the participant from the children to obtain consent. In these cases, with the permission of the research subject, we obtain consent in the presence of the children. Finally, with permission of the research subjects, husbands and wives are sometimes consented together. It is most culturally appropriate to be in the kitchen, dining or living room of the home and inappropriate to use a more private setting such as a bedroom or office. When at all possible, interactions will occur in a corner of the room, away from the activity of the family.

7 * Describe the provisions for assessing participant understanding:

All participants must be alert, oriented and be able to respond appropriately to questions during and after the consent discussion. The participant will be asked open ended questions about the purpose and risks of the study. Participants will be asked about voluntary nature of participation and what they would do if they wanted to withdraw or if they had an adverse event. If a subject cannot correctly respond to questions about the study, information will be reviewed again with the individual. If after review the subject cannot verbalize understanding, he/she will not be enrolled in the study. Amish liaisons may provide explanation in PA Dutch if necessary to aid understanding.

8 * Describe the consideration for ongoing consent:

This study involves one time sample collection and follow up survey or interview. At the time of survey or interview, participants will be reminded the purpose and voluntary nature of the research. They will be reminded that they may decline or withdraw from participation without any negative consequences.

HP-00081981 Waiver of Documentation of Consent_V2

Waiver of Documentation of Consent

You indicated that a waiver of documentation of consent (verbal/oral consent) is requested.

1 * Indicate why a waiver of documentation of consent is being requested for the study:

- ○ The only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality.
- ● **The research presents no more than minimal risk of harm to subjects, and involves no procedures for which written consent is normally required outside of the research context.**

2 * Provide a justification/explanation for the choice above:

Waiver of documentation of consent is requested for probands and family members who choose not to have genetic testing. The study procedures include return of completed surveys and possible interview about attitudes and experience with genetic testing. These procedures represent no more than risk individuals encounter in everyday life. All of the essential elements of informed consent are included in the information / consent letter sent with the questionnaires. If a potential participant agrees to complete the survey, they will return the letter indicating their agreement.

ID: VIEW4E1C6EF6F5000
Name: v2_Waiver of Documentation of Consent

HP-00081981 Children (Assent)_V2

Children (Assent)

You indicated that children are included in this study.

1 * From whom will assent be obtained?

- ○ All children
- ○ None of the children
- ● **Some children**

1.1 If assent will be obtained from some children, describe which children will not be asked for assent and why:

Written assent will be obtained from children 13-17 years of age. Younger children will have key points of the study explained in language understandable and appropriate to their developmental level and verbal assent will be obtained. For very young children and infants we will not obtain assent, but will not include any child who does not cooperate or seem unwilling to comply with the procedures.

2 * How will assent be documented? (*Answer "N/A" if assent will not be obtained from any of the children*)

A signed IRB-approved assent form will document assent for minors age 13-17. For all children, an informed consent note will document the consent process, parental permission and manner in which assent was obtained.

ID: VIEW4E1B2E37C1C00
Name: v2_Children (Assent)

HP-00081981 Waiver of Assent_V2

Waiver of Assent

1 * Why is a waiver of child assent being requested?

A waiver of assent is justified based upon the following:

- ○ 1. The research involves no more than minimal risk to subjects
  2. The waiver will not adversely affect the rights and welfare of the subjects
  3. The research could not practicably be carried out without the waiver; and
  4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
- ● **The capability of these children is so limited that they cannot reasonably be consulted (taking into account the ages, maturity, and psychological state of the children involved)**
- ○ The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research

2 * Provide a justification/explanation for the choice above:

A waiver of child assent is only being sought for those very young children who cannot reasonably be consulted.

HP-00081981 Consent Forms - Draft_V2

Consent and HIPAA Authorization Forms - Draft

1 Upload all of your Consent Forms for approval. Use only Microsoft Word.

Name	Created	Modified Date
Family consent(0.03)	11/8/2018 2:31 PM	2/18/2020 4:11 PM
Family assent(0.02)	11/8/2018 2:37 PM	2/18/2020 4:11 PM

IMPORTANT NOTE: the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, approved consent forms will be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

1A Archived Consent Forms:

Name	Created	Modified Date
There are no items to display		

2 Upload any HIPAA authorization forms here:

HIPAA for Cascade study 10.31.18.doc(0.02)	11/8/2018 2:38 PM	12/17/2018 10:43 AM

Please refer to HRPO's website for specific instructions for preparing informed consent documents and to access current templates: http://hrpo.umaryland.edu/researchers/consents.html

ID: VIEW4E1C7712D3000
Name: v2_Consent Forms - Draft

Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

1 **Department/Division Review** - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

Med Endocrinology

If this information is incorrect, please notify the HRPO office.

2 **RSC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Radiation Safety Committee may be required.

* 2.1 Does the research involve the use of ionizing radiation? ○ Yes ● **No**

2.2 Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory?

3 **IBC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Institutional Biosafety Committee may be required.

* 3.1 Does the research involve human gene transfer? ○ Yes ● **No**
-OR-
Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve the exposure of human subjects to pathogenic microorganisms, or the exposure of research staff to human subjects or samples known or reasonably expected to carry infectious disease(s)?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

4 **Cancer Center Criteria** - Answer the following to determine if review by the Cancer Center (Hematology-Oncology) may be required.

* Does the protocol involve in any way studies related to the prevention, treatment, diagnosis, or imaging of neoplastic diseases? ○ Yes ● **No**

5 **General Clinical Research Center Review Criteria** - the GCRC offers free and/or cost shared resources for patient-oriented research. Click Here for more information.

Answer the following to determine if review by the GCRC may be required.

* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct this activity? ○ Yes ● **No**

6 **VA Review Criteria** - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required.

* 6.1 - Will the research be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments)? ○ Yes ● **No**

* 6.2 - Will the research utilize VA resources (e.g., equipment, funds, medical records, databases, tissues, etc.)? ○ Yes ● **No**

* 6.3 - Will the research be conducted on VA property, including space leased to and used by VA? ○ Yes ● **No**

PLEASE NOTE that the research may be funded by VA, by other sponsors, or may be unfunded.

HP-00081981 Summary of Required Reviews_V2

Summary of Required Reviews (other than IRB)

1 **Additional Committee Reviews** - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission

This protocol has no related submissions (RSC, GCRC, IBC, etc)

2 **Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
Med Endocrinology	Complete
Pediatrics	Complete

ID: VIEW4E1C8D9AE4000
Name: v2_Summary of Required Reviews (other than IRB)

HP-00081981 Additional Documents_V2

Additional Documents

1

Upload all additional documents here:

Name	Created	Modified Date
ECG scheduling letter_070622.docx(0.01)	7/8/2022 2:46 PM	7/8/2022 2:46 PM
COVID-19 Ed Activity Book-11-final (1) (1).pdf(0.01)	5/24/2021 10:46 AM	5/24/2021 10:46 AM
arc newsletter 5.17.2021.pdf(0.01)	5/24/2021 10:25 AM	5/24/2021 10:25 AM
COVID risk statement(0.01)	12/9/2020 1:58 PM	12/9/2020 1:58 PM
LQTS COVID letter on letterhead_060820_clean.doc(0.03)	5/11/2020 4:39 PM	6/9/2020 11:22 AM
Family member questionnaire only consent letter rev 010520.docx(0.02)	1/7/2019 1:20 PM	1/5/2020 2:07 PM

ID: VIEW4E0962513A000
Name: v2_Additional Documents

HP-00081981 Final Page of Application_V2

Final Page of Application

You have reached the final page of this application. It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this page. The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will be routed to the following Departments for review prior to being forwarded to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	**Review Status**
Med Endocrinology	Complete
Pediatrics	Complete

Required Safety Committee Reviews - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission

This protocol has no related submissions (RSC, GCRC, IBC, etc)

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you, you must address their concerns and resubmit the protocol for review to all designated departments. After all departments have reviewed the application, it will automatically be sent to the IRB for review. Changes made to the submission after its approval must be submitted as modifications.

Investigator Attestation
By submitting this application, I, the Principal Investigator (PI), certify that the information provided in this application is complete and correct. Research will be conducted according to the submission as described, only by the approved principal investigator and study team members.

In addition, I agree to the responsibilities of a PI, including:

- Obtaining informed consent (if applicable) from all subjects as outlined in the submission.
- Reporting new information to the IRB per the requirements of the Investigator Manual.
- If Required, obtaining renewal of the protocol prior to the expiration of the approval period or halt all study activities upon study expiration.
- Accepting ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the project.
- Ensuring performance of all research activities by qualified personnel according to the IRB approved submission.
- Ensuring that research personnel have or will receive appropriate training.
- Ensuring no changes will be made in the research until approved by the IRB (except when necessary to eliminate apparent immediate hazards to subjects).

Click the "Finish" button and then click "Submit Application" in the submission Workspace.

ID: VIEW4E1B10C500000
Name: v2_Final Page of Application

STATISTICAL DESIGN AND STUDY POWER

A. Power Calculations

A1. Aim 1 (cascade screening intervention)

Our study is based on 70 *KCNQ1* Thr224Met probands who were identified as part of another research study and chose to undergo clinical confirmation of their genotype and clinical evaluation for long QT syndrome. We cannot approach probands who chose not to undergo the return of results process. These 70 probands have over 700 first degree family members who may be eligible for cascade screening with our intervention. We can assume some of the family members have died and some may not live in Lancaster County, but a very large proportion will be eligible for testing. Due to privacy laws we cannot approach a family member directly who has not first been contacted by the proband. We will provide family letters to probands for them to share with family members, but this is a personal decision for each proband. This study will compare the rate of uptake of cascade screening before and after our intervention of a simplified cascade screening program. Given that an individual who undergoes cascade screening before our intervention, during the 'traditional' period does not need to undergo testing again, we cannot statistically compare the difference in the proportion of family members who undergo cascade screening before and after the intervention or the statistical power that our study will have to detect a difference in uptake. That being said, our experience suggests that uptake of cascade screening will be very low among the Amish during the 'traditional' phase when cost, transportation, and an invasive test are barriers. This pilot study will test whether we can overcome these barriers and detect a *meaningful* improvement in uptake of cascade screening, disclosure to family members, and uptake of appropriate medical intervention. We will define this meaningful improvement *a priori* as a 15% improvement. For example, If we have 3% of eligible individuals undergo cascade screening during the traditional phase, we would deem 18% of eligible individuals getting tested a clinically meaningful increase. This would translate into 15/500 getting tested before our intervention and 87/485 getting tested after implementing our intervention. Another way of looking at this is that approximately 2-3 probands would initiate cascade screening before the intervention and 12-13 would after the intervention (assuming 7 children per proband).

A2. Aim 2 (proband and family interviews)

To further assess participants' experiences of receiving the result of *KCNQ1* p.Thr224Met testing, the goal of this second, qualitative phase is to elaborate on the results of Aim 1 through semi-structured, in-depth in-person interviews. Interview participants (adults only) will be sampled purposively to include roughly 30 probands and 45 family members. In order to maximize variability with respect to the genetic test results (e.g., positive and negative), whether or not they shared their results, and primary implementation outcomes (e.g., whether or not they underwent cascade screening), we will enroll 15 probands who shared results with family members, 15 probands who did not share results, 15 family members who underwent cascade screening and were mutation positive, 15 family members who underwent cascade screening and were mutation negative, and 15 family members who did not undergo cascade screening. The goal of this sampling strategy was to achieve maximum variation and minimal informational redundancy.[1] A guide for qualitative research is usually to include approximately 15 interviewees in order to obtain saturation and a homogeneous sample with maximum variation. Therefore, we expect to reach saturation and have a good representation of our participants.

B. Statistical methods with respect to each outcome

B1. Aim 1 (cascade screening intervention)

B1.1 Primary outcome

Our primary outcome is the rate of uptake of cascade screening before ('traditional') versus after ('simplified') the intervention. Uptake for this outcome is defined as the proportion of first degree family members (i.e. offspring and siblings) of the initial 70 probands who undergo cascade screening out of all eligible first degree family members (as defined by the Fisher book). We will compare the proportion before versus after the simplified screening approaches. Any individuals who undergo screening before the intervention will no longer be eligible for screening with the simplified cascade screening so the

denominator will decrease accordingly. We have chosen to use the denominator of all first degree relatives defined by the Fisher book because this number is not dependent on participants returning the surveys where they will provide information on how many family members they told (and how many they have). Our secondary outcome includes the proportion of informed relatives who get screened. The number of participants screened for all outcomes will be obtained from charts (as Dr. Streeten is ordering physician for all tests).

B1.2 Secondary outcomes

a. Extent of disclosure of genotype results before and after the intervention. This outcome is defined as the number of family members (siblings and children) told (reported via survey) out of the total number of proband first degree relatives (known from the Fisher Book and asked on the survey).
b. Proportion of informed first-degree relatives who get screened before and after the intervention. This outcome is defined as the number of family members tested out of the number told by probands (reported via surveys)
c. The overall rate of uptake of preventative therapy among probands and family members (e.g., see a cardiologist and/or take a beta-blockers)

Analyses of secondary outcomes (a) and (b) will occur in the same manner as the primary outcome, by comparing proportions before and after the intervention. For secondary outcome (c), we don't expect the proportion of appropriately treated carriers to be impacted by our intervention, but rather the absolute number of treated individuals would be impacted by detecting more carriers with improved cascade screening. For the disclosure outcome (a), we will compare results using the denominator based on Fisher book data and based on data reported in the survey. For the uptake of screening among those informed outcome (b), the denominator is based on the survey results (the proband will be asked who they disclosed results to and the family member will be asked if their family member told them). For the uptake of clinical recommendation outcome (c), we will use data from the participants' charts to determine whether beta-blocker therapy was indicated and prescribed. We will gather data from the survey on whether participants are following the recommendations. While we don't expect our intervention to change the proportion of individuals appropriately treated, we will compare the proportions before and after the intervention to confirm this assumption.

B1.3 Missing data

Based on the fact that our primary outcome data will come from tests ordered through Dr. Streeten, co-investigator, we expect very little missing data. For the secondary endpoints, we will rely on information obtained via surveys and will provide an incentive to encourage participants to complete the 2 surveys. In the case of missing data we will assess the types of missing data (random, random but not impacting dependent variables, or non-random). Our experience with the Amish suggests that once they commit to participate they will participate fully, so we do not anticipate a great deal of missing data. We have estimated that we will have an approximate 60% return rate of surveys based on previous data.

B2. Aim 2

The data collected from the Aim 2 interviews will be qualitative. All interviews will be audio recorded and transcribed. Transcripts will be imported into NVivo software. Interview data will be analyzed using a combined deductive and inductive approach. Questions from the interview guide will be used to develop an initial coding scheme, and inductive codes will be added as transcripts are reviewed and additional themes are noted. The first set of transcripts (N=5) will be initially independently coded by two members of the research team (Ms. Kristin Maloney and Dr. Yue Guan) to develop a consensus coding scheme. Once the coding scheme is being applied consistently, one member of the research team will code the remaining transcripts. These data will be independently reviewed by two other research team members and interviews will be halted when the entire research team agree that informational redundancy has been reached.

REFERENCES:

1. Sandelowski, M., *Sample size in qualitative research.* Res Nurs Health, 1995. **18**(2): p. 179-83.