Reporting Adult-Onset Genomic Results to Pediatric Biobank Participants and Parents (PRoGRESS)

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1.0 BACKGROUND AND SIGNIFICANCE:

The potential benefits and harms of returning genomic results to children and their parents are matters of enduring controversy—especially genomic results for adult-onset conditions that are not medically actionable in childhood (e.g., hereditary breast and ovarian cancer syndrome and Lynch syndrome). Returning results for conditions that are medically actionable in childhood can yield benefits to children and their parents. Proponents of returning results for adult-onset conditions highlight the potential for initiating life-saving preventive measures in parents who are found to carry the same genomic variant as their children. Moreover, the legal "loss of chance" doctrine might provide added justification for returning these results to guide healthcare for parents of the affected children. However, pediatricians, geneticists, and bioethicists have expressed concerns that children who receive a result for an adult-onset condition might experience negative psychosocial outcomes such as distress, discrimination, loss of future autonomy, or altered family functioning. Empirical data to inform either position in this controversy, however, are lacking. As a result, policy makers cannot make evidence-based judgments about the potential benefits and harms of returning genomic results related to adult-onset conditions to children and their parents.

The question of whether to return genomic results for adult-onset conditions to children has been hotly debated among pediatricians, geneticists and bioethicists. Exome- or genome-scale sequencing is used widely in clinical and research settings, both as a diagnostic tool and, in a few settings, as population screening in healthy individuals.[1,2] This testing provides an opportunity to query sequence data for pathogenic variants in medically actionable genes – those with increased disease risk and established interventions to reduce risk. However, there has been considerable debate about whether the opportunity to investigate these genes is in fact an ethical or legal obligation or even ethically or legally permissive. This is particularly true for variants that are not of immediate clinical utility, as in the case of genomic findings in children associated with adult-onset disease.[3,4] Mostly absent from the debate have been pediatric patients and their families—a perspective that is essential if one is committed to patient-centered care.

The debate began in earnest with the 2013 publication of the American College of Medical Genetics and Genomics (ACMG) guideline that recommended that clinicians notify their patients with an incidental, medically actionable genomic finding on genome-scale testing, regardless of the age of the patient.[5] Examples of medically actionable conditions include hereditary breast

and ovarian cancer (HBOC) syndrome (BRCA1/2 genes) and Lynch syndrome (MLH1, MSH2, MSH6 and PMS2 genes) and familial hypercholesterolemia (LDLR, APOB and PCSK9 genes), all of which have top-tier evidence for reducing morbidity and mortality.[6] Among the conditions listed by the ACMG as being sufficiently actionable to merit notification of patients who were found incidentally to have an associated variant, 28 can have pediatric onset or initiation of risk reduction procedures.[5,7] The two remaining conditions – HBOC and Lynch syndrome – do not typically lead to childhood onset of disease[5,7] and are managed accordingly, with recommended risk reduction postponed until adulthood.[8,9] Yet, the authors of the ACMG guidelines were compelled by the interests of adult relatives and of the children themselves. Identifying an adult-onset condition in a child could prompt relatives to be tested for a potentially life-threatening condition.[5,10] Preventing these life-threatening conditions in adults can also protect the interests of children under their care.[5,10]

The ACMG recommendation seemed to contradict long-standing guidance to defer testing for adult-onset genetic conditions until children reach adulthood and can decide whether to have testing.[11-14] These professional guidelines have focused on the best interest of children, citing concern about potential psychosocial harm and corresponding lack of clear medical benefit.[11-15] Proposed harms include psychological harms (e.g., increased distress, negative impacts on self-image); negative impact on family relationships (e.g., differential treatment by parents, including the 'vulnerable child syndrome'); discrimination; and failure to preserve autonomy (e.g., infringing upon a child's right to an open future).[11-13,16,17]

Others have countered that there might be benefits to returning adult-onset genomic findings to children. Beyond the ACMG's rationale,[5] proposed benefits include psychological benefits (e.g., opportunity for adjustment to hereditary disease), positive impact on family relationships, and promotion of autonomy.[17] Further, the limited available evidence has not borne out the negative psychosocial impacts anticipated by those opposed to the return of genomic information to children. Reviews of psychosocial outcomes in children who underwent genetic testing have not shown clear evidence of a negative impact.[18,19]

In contrast to professionals' concerns, parents and adolescents have expressed interest in receiving genomic findings that may not immediately impact a child's care.[20-23] Adolescents in one study of stakeholders' views of reporting results from genome-scale sequencing expressed interest in adult-onset results and in being involved in decision making about whether to learn

these results.[23] Half of a sample of British adults felt that parents should be able to test their children for adult-onset conditions, even though some acknowledged that commonly stated reasons for deferring such testing to adulthood (e.g., stigma, fear of discrimination) were valid reasons.[22] In other studies, parents have expressed interest in their children receiving adult-onset genomic results even if those results are not medically actionable.[20,21] Parents have described that researchers have a responsibility to notify them of secondary genomic findings from research testing of their children, even of for untreatable adult-onset diseases like Huntington disease.[21]

This interest among children and parents in learning adult-onset genomic findings is consistent with our preliminary studies. First, several members of the Geisinger Precision Health Youth Advisory Council of local 14- to 17-year-olds, most of whom are female, have expressed an interest in learning adult-onset genomic results (e.g., pathogenic *BRCA1/2* variants). Second, we convened focus groups of parents of pediatric participants in Geisinger's MyCode Community Health Initiative (a genomic biobank linked to electronic health record data) to assess their interest in receiving results for their children for an adult-onset condition such as Lynch syndrome. These focus groups used a deliberative engagement format and case scenarios to help parents understand professional organizations' perspective and react to a hypothetical scenario of receiving a Lynch syndrome result for their child. Nearly all participants wanted Lynch results for their children, saying that the importance of these results to their children's future health outweighed the right of children to make their own testing decisions once they reach adulthood.[24] Consistent with similar research,[21] parents proposed that some families would benefit from additional counseling to accompany the disclosure of results. Finally, we analyzed essays written by high school students for the 2016 American Society of Human Genetics (ASHG) DNA Day Essay Contest. Students were asked to name an adult-onset genetic condition and defend or refute the 2015 ASHG recommendation to defer testing for adult-onset conditions until adulthood.[13] Of the 205 students who wrote about HBOC syndrome, 56% argued for *BRCA1/2* testing before adulthood, citing reasons such as prevention and life planning.[25]

In addition to these psychosocial and healthcare utilization concerns about informing children and their parents about adult-onset findings, deciding whether to disclose findings may have legal implications. Genetic professionals have long been concerned about legal liability,[26] including risk for liability associated with researchers' decisions to return findings to or withhold them from individual participants. In a traditional tort action, a plaintiff must prove that there

was a breach of a duty (or failure to act according to the applicable standard) that caused an injury. The "loss of chance" doctrine is a legal theory[27] available in some states that enables a plaintiff to recover money from a defendant whose breach of duty caused a reduction in the chance of a favorable outcome (such as a delayed diagnosis resulting in a diminished chance of recovery from a pre-existing medical condition).

There is a paucity of critical analysis of the "loss of chance" doctrine as it relates to genomic research and medicine, particularly regarding returning or postponing the return of adult-onset genomic findings to children. This is despite the acknowledgement by some scholars of its relevance to the issue of secondary (or additional[28]) genomic findings.[26,29] While the "loss of chance" doctrine made its first court appearance 50 years ago[30] and its first law journal appearance 35 years ago,[31] there remain very few entries in PubMed. The American Law Institute, which issues Restatements "to clarify, modernize, and otherwise improve the law,"[32] has not yet taken a position on the doctrine.[33] This legal doctrine is poorly understood under any fact pattern or scenario in the context of returning adult-onset findings to children and manifested differently across the states[34-37] (often with a commingling of distinct concepts of causation and valuation of compensable damages).[31] Therefore, conclusions about the doctrine's applicability to genomic medicine broadly or to the debate over returning adult-onset genomic findings to children specifically cannot be drawn from general legal discussions.

A dearth of empirical data has prevented resolution of the debate over returning adult-onset genomic findings to children. The available evidence of children's psychosocial outcomes is limited by the small number of studies; a focus on pediatric-onset conditions; methodological differences that hinder comparisons; and a lack of longitudinal follow-up that would facilitate a clear understanding of how adult-onset genomic findings impact children and families over time.[18,19,38] There is broad recognition of this lack of data[12,39] and strong support for using data to resolve the debate and develop best practices.[11,38,40]

2.0 OBJECTIVE AND AIMS:

Our program's long-term goal is to determine how best to use genomic information to guide care over the course of a child's development in ways that maximize the physical and psychosocial health of children and their families. As one of the first empirically driven studies designed to achieve this goal, we propose to assess the psychosocial, behavioral, and legal impact of disclosing adult-onset genomic findings to children and their parents. Leveraging our experience

in returning medically actionable genomic findings to adults enrolled in Geisinger's MyCode Community Health Initiative, we will augment the existing Genomic Screening and Counseling program with support from clinical psychologists and social workers with expertise in pediatric and adolescent development. Based on available literature on the impact of informing children about their genetic condition or their hereditary breast cancer risk, and on our preliminary studies with parents of pediatric MyCode participants, we anticipate that there will be no difference in primary psychosocial outcomes between adolescents and parents who receive an adult-onset finding compared with those who receive a pediatric- onset finding or those who do not receive a genomic finding. Testing this hypothesis will provide a previously unavailable evidence base for programs that are wrestling with whether, or how, to disclose genomic results related to adult-onset conditions to children and families.

This study will be conducted via two pathways for enrollment - retrospective and prospective. The prospective approach involves recruiting pediatric MyCode participants with an expected genetic testing result and their parents before confirming the result via clinical genetic testing (as described in the grant proposal). The retrospective approach involves beginning with contacting MyCode adult participants who have a clinically confirmed genetic test result (also known as MyCode probands) and recruiting their pediatric relatives (who may not be MyCode participants or even Geisinger patients). We will conduct a longitudinal, mixed-methods cohort study of primary and secondary psychosocial outcomes among pediatric participants and their parents, and health behaviors related to receiving an adult- or pediatric-onset genomic result. Data will be gathered via quantitative surveys using validated measures of distress, family functioning, quality of life, body image, perceived cancer/heart disease risk, genetic counseling satisfaction, genomics knowledge, and adjustment to genetic information. Data will also be gathered via qualitative interviews with adolescents and parents; electronic health record review, and self-reported performance of risk reduction behaviors.
We will also conduct empirical and theoretical legal research to examine the loss of chance doctrine and its applicability to genomic research. In so doing, we will provide urgently needed empirical data regarding the psychosocial and behavioral impact of returning adult-onset genomic findings that will inform debates about whether children and families should be notified of such findings. The legal analysis will provide important context to further inform policy discussions, clarifying legal pressures that, if unaddressed by experts in ethical, legal and social implications, could require return of all findings regardless of timing of disease onset.

The proposed study will address the following related, but not overly dependent, aims.

Aim 1: Determine whether anxiety, depression, family functioning, and health-related quality of life differ at 12 months post-disclosure among adolescents and parents who: 1) receive an adult-onset result; 2) receive a pediatric-onset result; or 3) do not carry a familial variant.
Aim 2: Assess performance of recommended risk management behaviors among adolescent participants with a pediatric-onset result.
Aim 3: Analyze the applicability of the "loss of chance" tort doctrine to policies regarding the return or deferral of adult-onset genomic results to children.

Data from this innovative landmark study will inform policies and practices on national and international groups who are developing plans for performing genome-scale testing of children.

3.0 PROCEDURES:

3.1 Overall Research Design

We propose a longitudinal, observational cohort study using mixed methods to compare change in psychosocial outcomes and health behaviors among three study groups of pediatric participants and their parents.

1. Group 1 - those with a pathogenic variant in a gene associated with adult onset of disease (n=37 adolescents, 112 parents)
2. Group 2 - those with a pathogenic variant in a gene associated with pediatric onset of disease or with risk reduction interventions that begin in childhood (n=37 adolescents, 112 parents)
3. Group 3 - those who do not carry the familial variant (n=37 adolescents, 112 parents)

Patient identification and enrollment will use methods that are HIPAA-compliant, IRB-approved and recommended by the MyCode Ethics Advisory Council. The Council membership includes Geisinger patient representatives and nationally recognized bioethicists with expertise in genomic medicine, one of whom is a pediatrician. Both retrospective and prospective enrollment will include an informed consent visit in which psychosocial variables such as anxiety and depression will be assessed via a baseline survey among parents and adolescents at enrollment (T1). Consistent with Geisinger policy, children ages 7-17 will be asked to give assent to participate. If a child does not want to assent to participate, he or she will not be enrolled into the study (regardless of their parents' preference regarding enrollment). Parents of children who do not give assent will be ineligible to participate. Parent-participants will be asked to assess psychosocial outcomes for themselves and for their children. Consistent with co-investigator Angela Bradbury's research on the experience of adolescent girls from families at increased risk for breast

cancer,[42] pediatric participants ages 11-17 years at enrollment (or who age into this adolescent age group) will also participate in quantitative surveys and qualitative interviews.

Pediatric participants (and potentially their untested parents) in the retrospective cohort will be offered cascade genetic testing as part of this study. Consistent with the original grant proposal, clinical confirmation of the expected pathogenic variant detected via MyCode sequencing will be a condition of enrollment for the prospective cohort. The outcome of the cascade genetic testing (for the retrospective cohort) or clinical confirmation testing (for the prospective cohort) will be disclosed during a disclosure visit with a genetic counselor. During this visit, genetic counselors will observe the participant's reaction and will perform a psychosocial assessment. Genetic counselors are experts in conducting psychosocial assessment and brief psychosocial counseling. The study Clinical Psychologists will review the genetic counselor's approach to psychosocial assessment and provide input in accord with the Psychologists' expertise. During the disclosure visit, the Genetic Counselor will provide participants with contact information for the study Clinical Psychologists. Participants can reach out to the clinical psychologists if and whenever they feel necessary during the study. The study Clinical Psychologists will conduct therapeutic consults as needed and conduct periodic psychosocial assessments of adolescent participants with adult-onset results. The study Clinical Psychologists will also do a 1-month check-in (after T2 data collection) for psychoeducation and mood check for all participants in groups 1 & 2. Validated surveys will be used to measure outcomes (Table 1) in each study group at 1 month (T2), 6 months (T3), and 12 months (T4) post-disclosure visit. We will conduct qualitative interviews with a subset of at least 45 participants in each of the two study groups who receive a genomic result to better understand the lived experience of adolescents with an actionable genomic finding and their parents. Data collection will continue after the grant funding ends because of Geisinger Research Division's commitment to following the study cohort. To address the legal specific aim, Dr. Wagner will lead the study team's legal experts in examining and monitoring the loss of chance doctrine in medical malpractice cases in federal and state courts across the United States and in monitoring legislative developments relating to the loss of chance doctrine as it applies to returning adult-onset genomic results to children.

Table 1. Outcomes, covariates, time points and validated measures in quantitative surveys.

Data Collection Method	Domain	Validated Measure	Time Points	Completed By
Aim 1 – Psychosocial Outcomes among Study Groups				

Quantitative survey	**Outcomes – All Groups**			
	General anxiety and depression*	• Assessment of symptoms of DSM-IV anxiety and depression in children (55) • Hospital Anxiety & Depression Scale (58)	T1, T2, T3, T4	P/A
	Family functioning and cohesion*	General Functioning subscale (short form) of McMaster Family Assessment Device (59)	T1, T2, T3, T4	P/A
	Health-related quality of life*	CDC HRQOL– 4 (56)	T1, T2, T3, T4	P/A
	Body image	Body Image Scale (60)	T1, T2, T3, T4	A
	Self-esteem	Rosenberg Self-Esteem Scale (61)	T1, T2, T3, T4	A
	Decision regret	Decision Regret Scale (62)	T2, T4	P
	Patient satisfaction	Genetic Counseling Satisfaction (63)	T2	P
	Family communication	Family communication of genetic test results (66)	T2, T4	P
	Covariates – All Groups			
	Psychological flexibility	• Acceptance and Action Questionnaire – II (64) • Avoidance and Fusion Questionnaire for Youth(65)	T1, T2, T3, T4	P/A
	Family communication	Family communication of genetic test results	T2	P
	Lifestyle behaviors	□ Physical activity, diet, smoking and vaping (67) □ Alcohol consumption (57)	T1, T3, T4	A
	Information seeking	Health Information Orientation Scale (68)	T1	P
	Personal utility	Perceived utility of whole genome sequencing (69)	T1, T2, T3, T4	P
	Perceived risk	Perceived cancer/heart disease risk (43, 70)	T1, T2, T3, T4	P/A
	Health literacy	Brief health literacy scale (71)	T1	P
	Genomic Literacy	Knowledge of genome sequencing (72)	T1	P
	Outcomes – Participants with Genomic Result – Groups 1 and 2			
	Condition specific distress	Children's Revised Impact of Events Scale (75)	T2, T3, T4	P/A
	Adjustment to genetic information	Psychological adaptation to genetic information scale (74)	T2, T3, T4	P

	Patient education and empowerment	Health Education Impact Questionnaire (76)	T2, T3, T4,	P
Qualitative interview	Constructs for which validated measures do not exist (e.g. vulnerable child syndrome, right to an open future)	N/A	T2, T4	P/A
Psychosocial assessment			Disclosure Visit	P/A
Observation of reactions to disclosure			Disclosure Visit	P/A
Aim 2 – Risk reduction Initiation among Group 1 and 2 Parents				
Quantitative Survey	**Initiation of risk management behaviors***	Adapted from risk management in unaffected women with pathogenic *BRCA1/2* variants (73)	T4	P
EHR Review	**Initiation of risk management behaviors***	N/A	T4	

***Primary outcomes,** T1=baseline; T2= 1-month post-disclosure; T3=6-months post-disclosure; T4=12- months post-disclosure, P=Parent of minor (ages 0-17), A=Adolescent (ages 11-17).

3.2 Detailed Study Procedures:

3.2.a. Retrospective Recruitment

For retrospective recruitment, we will ascertain study participants via adult MyCode probands, offer cascade testing to their minor relatives who have not had testing for a familial variant, and assign them into one of the three groups based on their result. At least one parent will participate for each pediatric participant. If the parent is a non-proband and has not undergone genetic testing for the family variant, the genetic counselor may offer genetic testing to the parent even before offering genetic testing to the child, as indicated. We will then assess psychosocial outcomes among adolescents (and parents) who receive an adult-onset result (group 1), pediatric-onset result (group 2), or do not carry the familial variant (group 3). We will also assess self-reported risk management behaviors among adolescents with a pediatric-onset result (group 2).

Following the informed consent visit, psychosocial variables such as anxiety and depression will be assessed via a baseline survey among parents and adolescents at enrollment (T1). Participants will then be scheduled for a pre-test visit with a genetic counselor via telemedicine (with in-person appointments available per patient request). If the participant agrees to proceed with genetic testing after speaking with a counselor, they will provide either a buccal sample or blood sample for analysis. About a month later, the participant's result (positive or negative) will be returned to the genetic counselor, who will

then conduct a telemedicine or in-person disclosure visit with the participant and their parent(s). During this visit, genetic counselors will observe the participant's reaction and will perform a psychosocial assessment.

3.2.b. Retrospective Study Population:

The study sample will be drawn from all pediatric (ages 0-17 years) relatives of MyCode probands with an autosomal dominant condition and their parents. Both Geisinger and non-Geisinger minor participants are eligible for participation via the retrospective pathway. At least one parent will be enrolled for each pediatric participant. Parents of children ages 0-10 years at enrollment will participate in data collection; parents of children ages 11-17 years at enrollment and their children will participate in data collection.

Table 2: Ascertainment and Eligibility for Retrospective Enrollment

Procedure	Revised
Ascertainment	Begins with MyCode adult participant with clinically confirmed adult- or pediatric consent variant
Eligibility – MyCode status	Minor relatives of MyCode adult probands and minors' parents
Eligibility – Geisinger patient status	Includes Geisinger and non-Geisinger minor participants
Eligibility – genetic conditions	Autosomal dominant conditions on MyCode genomic screening list are eligible (excludes hereditary hemochromatosis, *MUTYH*-associated polyposis, Wilson disease)

Inclusion Criteria:

- Any pediatric relative of a MyCode proband who has received an autosomal dominant result and at least one of their parents.

Exclusion Criteria:

- Individuals who have already had genetic counseling for any of the actionable target conditions as part of their routine clinical care or participation in other research.
- Relatives of MyCode probands who are deceased or have withdrawn from MyCode will not be contacted for this study.

3.2.c. Retrospective Enrollment Procedures:

1. Study staff will send adult MyCode probands who have received a result in an autosomal dominant condition (which excludes *MUTYH* and *HFE* genes) an online REDCap survey via the Patient Portal or email to determine whether they have minor relatives who have not had cascade testing for the familial genetic variant. Staff will not contact any MyCode probands who are deceased, have withdrawn from the study, or have asked not to be contacted (minimize contact group). Study staff (or the survey core group) will call MyCode probands who do not have a Patient Portal or email to determine if they have any eligible relatives that may be interested in the study. The survey will include the study phone number in the introduction text of the survey to give probands the option to call the study team directly if they do not wish to enter their relative's information online. The survey will ask the proband if they have any of the following relatives who have not been tested for the familial variant: o Minor children o Adult children with minor children o Minor siblings o Minor nieces or nephews
   If the proband does have any of the minor relatives listed above, the survey will ask for the contact information for those minor's parent/guardian (such as name, address, email, and phone number).
2. Study staff or the survey core group may call probands who do not complete the survey (or partially complete) to complete the survey over the phone. If the proband then states that they have eligible untested minors, the survey core staff will proceed to offer a telemedicine appointment with a research assistant to discuss the study further.
3. As survey responses are returned, study staff will send the parents of these potential participants a study introduction letter via a Patient Portal message, email, or mailed letter that describes the study, including a copy of the elements of informed consent, and an opportunity to opt out from any further contact.
4. About two weeks after study introduction letters are sent, Geisinger's Survey Research Core will call those potential participants who have not opted out and offer a telemedicine appointment to discuss a study on their beliefs about MyCode and receiving genomic results. In person consenting appointments may also be available per patient request.
    - If the participant agrees to attend a consenting visit, the Survey Core team will:

- Schedule the consenting visit with the study team's research assistants using a shared calendar.
- Collect the participant's email address. This will be required for participants who choose to complete a telemedicine visit in order to send the telemedicine appointment invitation.

- If the potential participant declines to participate in the study, the Survey Core member will ask the participant if they mind sharing why they are declining and will thank them for their time (see the revised recruitment phone script attached under study documents).

5. Research assistants will be responsible for leading the telemedicine and in-person consenting visits. If the participant agrees to participate after learning about the study, research assistants will obtain written documentation of consent during the study visit.
    - For in-person visits, the participant will sign two hard copies of the consent form and will keep one of the copies for their records. Children of assenting age (7-17 years) will also be required to sign the paper forms if they agree to assent.
    - For telemedicine consenting visits, the participant will provide their e-signature via a Geisinger-approved platform (e.g the InTouch platform approved for telehealth visits). Research assistants will explain the study, answer any questions the participant may have, and will share their computer screen so that they can review the consent form via the screen sharing feature. Children of assenting age (7-17 years), will also be asked to attend the telemedicine visit and sign the online form if they assent, with the research assistant as a witness. A PDF archive of the participant's signed consent form will then be saved electronically and will be sent to the participant through the Patient Portal or email.
6. During the consenting appointment, consenting parents and assenting adolescents ages 11-17 years will be asked to complete a brief baseline survey (T1) assessing psychosocial outcomes and health behaviors and beliefs. If the visit is conducted in person, the survey will be completed on an iPad. If the visit is completed via telemedicine, the survey will be sent securely via email through REDCap for the participant to complete. The parent and adolescent participant will complete the survey during the telemedicine visit (privately and separately) so that study staff can assist if the participant has questions or technological issues. After completing the baseline

survey, participants will be scheduled for a pre- test visit with a genetic counselor prior to ending the telemedicine visit.

Participants who live outside of the state of Pennsylvania will not be scheduled to see a Geisinger genetic counselor due to state licensure laws. Instead, our study team will refer that patient to Genome Medical™ to continue with pre-test counseling and potential genetic testing. Genome Medical™ is a genetic counseling company made up of counselors and physicians with licensures in all US states. Following the participant's consent, Geisinger study staff would upload the participant's name, date of birth, gene, variant of interest, and contact information into Genome Medical's secure platform. The Geisinger study team will then immediately schedule the participant within the Genome Medical portal to see one of their genetic counselors at a date and time that is convenient. Genome Medical staff will send the participant an email with their appointment information and will conduct genetic counseling and testing for the participant.

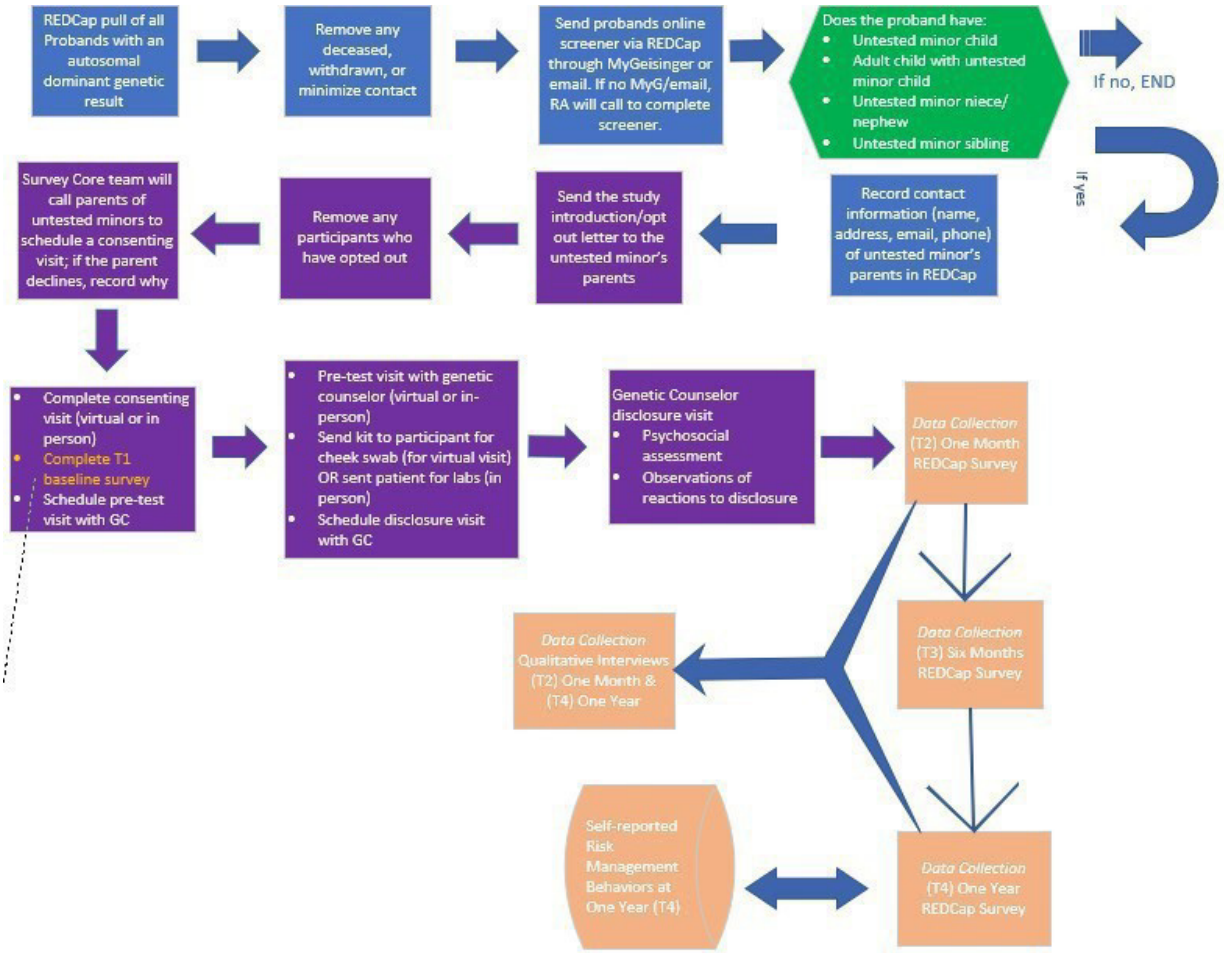
7. During the pre-test visit with the genetic counselor (at Geisinger or Genome Medical), the counselor will review the procedure for cascade testing and will review the possible testing outcomes (i.e., positive or negative for familial variant). If the parent and child (of assenting age) agree to proceed with cascade testing for the child, the counselor will obtain a blood or buccal sample in clinic, via home phlebotomy, or via a lab kit (for saliva). They will schedule a genetic counseling disclosure visit (either in person or via telemedicine, per participant's preference and regular clinical genetic counseling practice) in about one month, which will allow sufficient time for clinical confirmation of variants.
8. Participants in group 1 and 2 will take part in a genetic counseling visit via telemedicine (using the Geisinger-approved telehealth platform or Genome Medical's telehealth platform) or in-person per the participant's request. During this visit, participants in groups 1 and 2 will learn of their result (see Result Disclosure Procedures on page 11). Participants in group 3, those with a negative result, will be notified of their group status via a telephone call or a Patient Portal message.
9. Following the genetic counseling disclosure visit, data collection will continue via REDCap surveys at specified timepoints, qualitative interviews, and electronic health record review (or self-report) of health behaviors associated with the genetic result. (See

detailed study procedures for more information). Group 3 participants will only participate in survey data collection.

*MyCode probands may also be referred to the PRoGRESS study through the MyCode Genomic Screening and Counseling program at the time of their MyCode result disclosure. If a proband expresses interest in pursuing cascade testing for their child, the genetic counselor will introduce the PRoGRESS study to the patient. If the patient wants to learn more about the PRoGRESS study, the genetic counselor will contact the study team so that they can directly call the patient to schedule a consenting visit (step 5 above).
Additionally, through our partnership with Genome Medical, out of state relatives of MyCode probands who are seen by a Genome Medical genetic counselor will be provided a study information letter and will be directed to contact the study team by phone if they are interested in learning more and/or participating in PRoGRESS.

Parents and adolescents who have consented to join the study but have not submitted a sample for testing and therefore have not had a disclosure visit with a genetic counselor will receive modified surveys at 6 and 12 months after their initial pre-test visit.

Figure 1: Retrospective Enrollment Flowchart



3.2.d. Prospective Recruitment

Prospective recruitment for this study begins when a pediatric MyCode participant has a potential result in a gene that is on the Geisinger clinical return list. The study team will approach potential participants prior to clinical confirmation of any suspected pathogenic variants (i.e., after bioinformatic identification of a suspected pathogenic variant but before clinical confirmation of the variant's pathogenicity).

3.2.e. Prospective Study Population

The study sample will be drawn from all pediatric (ages 0-17 years) MyCode probands with a suspected genetic result and their parents as well as age and sex matched controls and their parents. At least one parent will be enrolled for each pediatric participant. Parents of children ages 0-10 years at enrollment will participate in data collection;

parents of children ages 11-17 years at enrollment and their children will participate in data collection.

Inclusion Criteria:

- Any pediatric MyCode proband who has a suspected autosomal dominant result and at least one of their parents.
- Age- and sex-matched pediatric MyCode participants (who have not received a result) and at least one of their parents ***Exclusion Criteria:***
- Individuals who have already had genetic counseling for any of the actionable target conditions as part of their routine clinical care or participation in other research.
- MyCode probands who are deceased or have withdrawn from MyCode will not be contacted for this study.

3.2.f. Prospective Enrollment Procedures:

1. Variant scientist will ask the Data Broker for a list of potential pediatric participants who have had a suspected pathogenic variant detected.
2. Variant scientist will confirm that the participant is eligible for variant confirmation.
3. Variant scientist will update a shared folder excel sheet with potential participants demographic and sample information.
4. Research assistants will send the parents of these potential participants a letter via the Patient Portal, email, or mail that describes the study, including a copy of the elements of informed consent, and an opportunity to opt out from any further contact.
5. About two weeks after this letter is sent, Geisinger's Survey Research Core will call those potential participants who have not opted out and offer a telemedicine or in- person appointment to discuss a study on their beliefs about MyCode and receiving genomic results.
    - If the participant agrees to attend a consenting visit, the Survey Core team will:
        - Schedule the consenting visit with the study team's research assistants using a shared calendar.
        - Collect the participant's email address. This will be required for participants who choose to complete a telemedicine visit in order to send the telemedicine appointment invitation.

- If the potential participant declines to participate in the study, the Survey Core member will ask the patient if they mind sharing why they are declining and will thank them for their time (see the revised recruitment phone script attached under study documents).
- If parents decline participation and their child is suspected to have a pathogenic adult-onset result, the study team's variant scientist will have their child's sample held for clinical confirmation until the child reaches age 18 years.
- If parents decline participation and their child is suspected to have a pathogenic pediatric-onset result, the variant scientist will proceed to clinical confirmation of the result and, if confirmed, follow the established clinical return procedure. This recruitment approach is consistent with the MyCode philosophy of notifying participants of actionable findings.[41,43]

6. Research assistants will be responsible for leading the telemedicine and in-person consenting visits. If the participant agrees to participate after learning about the study, research assistants will obtain written documentation of consent during the study visit.
    - For in-person visits, the participant will sign two hard copies of the consent form and will keep one of the copies for their records. Children of assenting age (7-17 years) will also be required to sign the paper forms if they agree to assent.
    - For telemedicine consenting visits, the participant will provide their e-signature via a Geisinger-approved platform (e.g the InTouch platform approved for telehealth visits). Research assistants will explain the study, answer any questions the participant may have, and will share their computer screen so that they can review the consent form via the screen sharing feature. If the participant agrees to consent in the study, they will provide their signature directly on the consent form using their mouse. Children of assenting age (7-17 years), will also be asked to attend the telemedicine visit and sign the online form if they assent, with the research assistant as a witness. A PDF archive of the participant's signed consent form will then be saved electronically and will be sent to the participant through the Patient Portal or email.
7. During the consenting appointment, consenting parents and assenting adolescents ages 11-17 years will be asked to complete a brief baseline survey (T1) assessing psychosocial outcomes and health behaviors and beliefs. If the visit is conducted in person, the survey will be completed on an iPad. If the visit is completed via telemedicine, the survey will be sent securely via email through REDCap for the participant to complete. The parent and

adolescent participant will complete the survey during the telemedicine visit (privately and separately) so that study staff can assist if the participant has questions or technological issues.

8. For prospective enrollees, we may require an additional MyCode blood sample from the child if there is not a sufficient sample in the MyCode biobank. This sample will be drawn and paid for by MyCode. Note: Obtaining an additional MyCode blood sample is covered under the MyCode protocol (IRB# 2006-0258).
9. After completing the baseline survey, participants will be scheduled for a genetic counseling disclosure visit (either telemedicine or in-person, as per patient's preference and regular clinical genetic counseling practice) in one month, which will allow sufficient time for clinical confirmation of variants in Groups 1 and 2 participants.
10. Participants in group 1 and 2 will take part in a genetic counseling visit via telemedicine (using the Geisinger-approved telehealth platform) or in-person per the participant's request. During this visit, participants in groups 1 and 2 will learn of their result (see Result Disclosure Procedures on page 11). Participants in group 3 will be notified of their group status via a telephone call or Patient Portal message.
11. Following the genetic counseling disclosure visit, data collection will continue via REDCap surveys at specified timepoints, qualitative interviews, and electronic health record review (or self-report) of health behaviors associated with the genetic result. (See detailed study procedures for more information). Group 3 participants will only participate in survey data collection.

Figure 2: Study Groups Prospective Enrollment

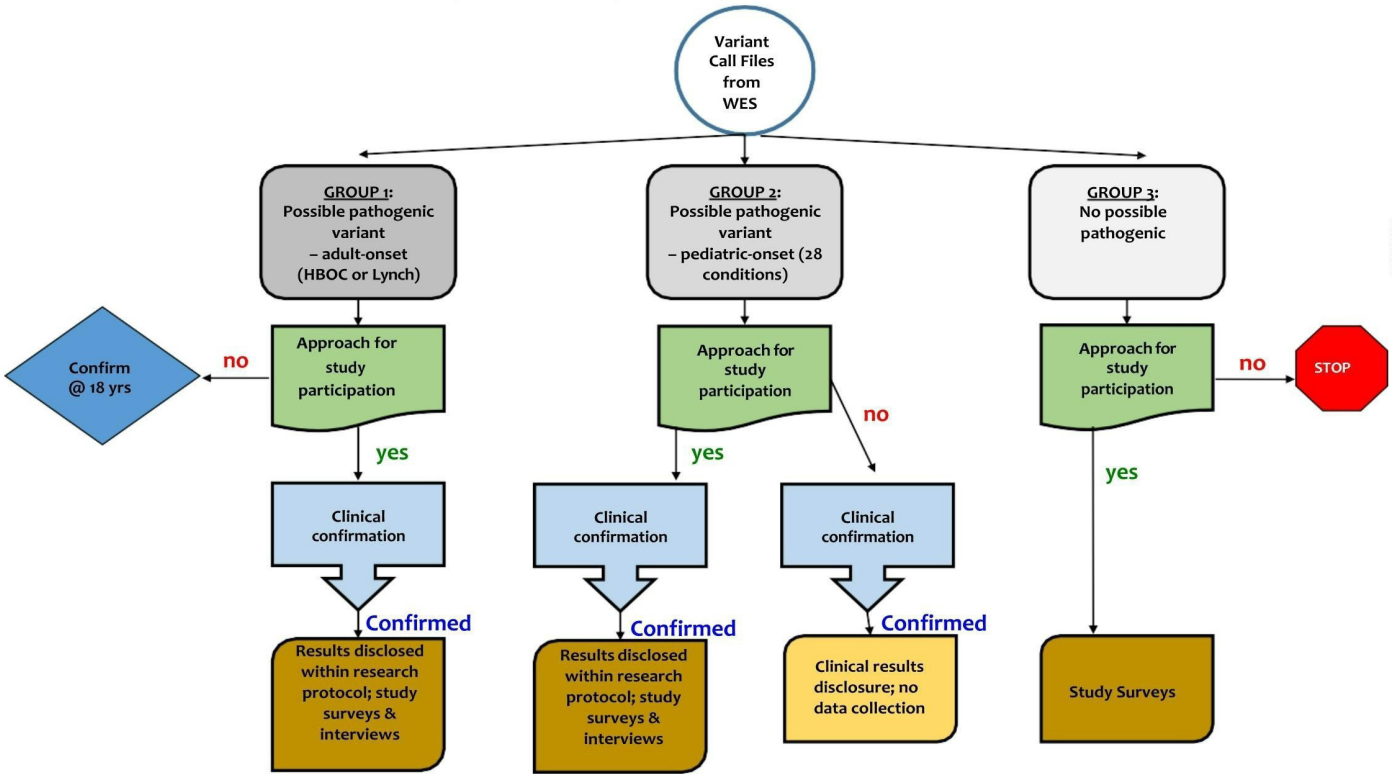
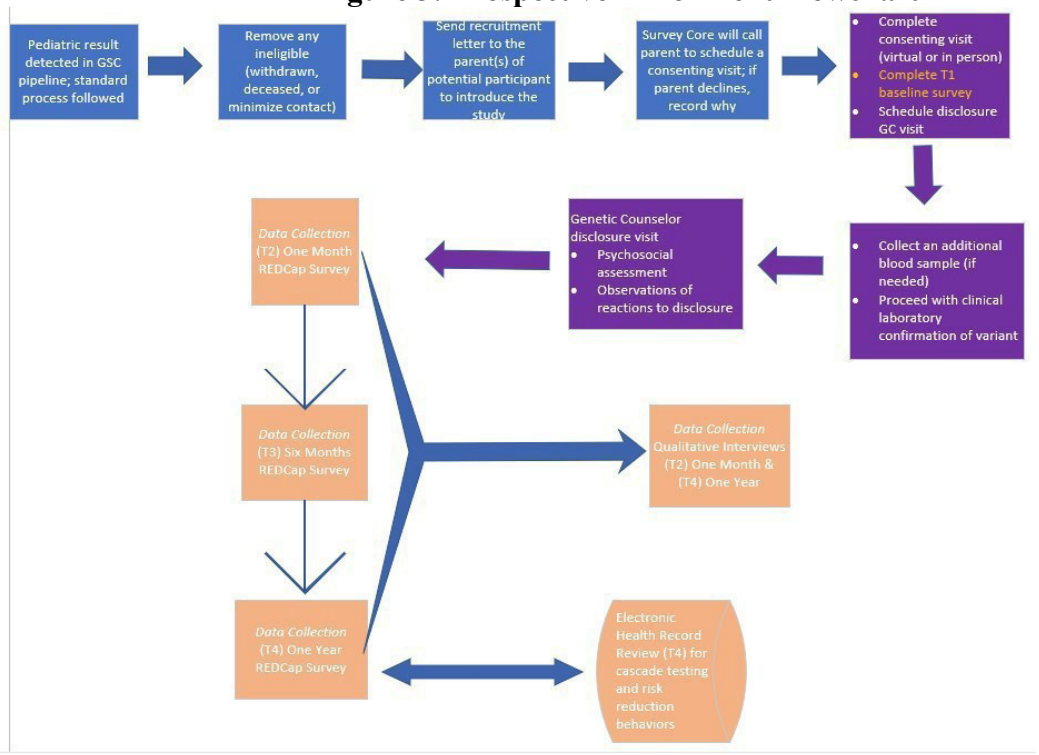


Figure 3: Prospective Enrollment Flowchart



3.3 Result Disclosure Procedures (Retrospective and Prospective)

Parents of pediatric participants with a clinically confirmed pathogenic result in one of the actionable genes of interest will learn of their result in an in-person or telemedicine consultation conducted by a genetic counselor. Telemedicine appointments through the Geisinger-approved system or Genome Medical's telehealth platform allow the patient and counselor to join the visit from home, but still provide face to face care. We will disclose results to all pediatric participants who have assented to the study. If a child is of the age of assent and not present at the initial disclosure visit, the study team will work with the participants parent(s) to disclose the result to that child at a later date.

We will ask parents for guidance on how to disclose results to their assenting children (e.g., at the initial disclosure consult or at a separate consult). As is standard of care in genetic counseling,[44] discussion of the result will include medical interpretation of the result and associated risk management recommendations; referrals of patients to the appropriate clinicians

for medical evaluation and, when indicated, initiation of risk reduction procedures; provision of emotional support; and a recommendation to encourage family communication of results and cascade testing. Given published concerns about psychosocial adjustment to this genomic risk information,[11-17] one of the study Genetic Counselors (or one of Genome Medical's genetic counselors) will perform a psychosocial assessment and will schedule separate therapeutic interactions with patients who exhibit clinically significant distress. The pediatric clinical psychologist will coordinate meeting at least every three months with all adolescents with an adult-onset genomic result and address any clinically significant distress per his standard clinical practice. These quarterly study visits will be covered by the study for the duration of the study. If the patient and psychologist decide to continue care outside of this study once it is over, they can do so but it will be considered routine care. We will also offer adult participants regular consults with the study's adult clinical psychologist.

Consistent with current practice among Geisinger genetic counselors returning genomic findings to adults, the study genetic counselor will contact parents at one- and six-months post-disclosure to assess ongoing informational and support needs.

Because study clinical psychologists do not have licenses to practice outside the state of Pennsylvania, Genome Medical genetic counselors will manage any instances of psychological distress in out-of-state participants per Genome Medical's standard practice, which includes coordinating care with a local psychologist.

4.0 DATA COLLECTION:

Data will be gathered from all study groups via quantitative surveys using validated measures of distress, family functioning, quality of life, body image, perceived cancer/heart disease risk, genetic counseling satisfaction, genomics knowledge, and adjustment to genetic information. Data also will be gathered via qualitative interviews with adolescents and parents; electronic health record review, and self-reported initiation of risk reduction behaviors among Group 2 participants and parents. Group 3 participants will not be included in interviews or electronic health record review. Additionally, consented parents and adolescents who have not submitted a sample for testing will receive modified surveys at 6 and 12 months after their pre-test visit.

We will also conduct empirical and theoretical legal research to examine the loss of chance doctrine and its applicability to genomic research.

We will use a mixed-methods data collection approach. Quantitative surveys using validated

measures of relevant psychosocial outcomes will be administered to participants in each study group at in-person or telemedicine enrollment and at 1 month, 6 months and 12 months post-disclosure visit. Surveys will be administered via participants' preferred method, i.e., phone, online, or paper. We will conduct qualitative interviews with a subset of at least 45 participants each in the two study groups who receive a genomic result to better understand the lived experience of adolescents with an actionable genomic finding and of their parents. These interviews will be conducted at 1 month and 12 months post-disclosure. We will also query the electronic health record (EHR) when possible (for Geisinger patient-participants) and will assess the initiation of self- reported risk reduction behaviors among Group 2 participants and parents. Geisinger study staff will have access to Genome Medical's patient portal for those out of state study participants to review any data, such as result disclosure information or referrals.

4.1 Data Collection Procedures

To ensure a high response rate, surveys will be offered via multiple modalities, including phone, Internet, and paper (if requested). At enrollment (T1), 1 month (T2), 6 months (T3), and 12 months (T4) post-disclosure consultation, a secure REDCap link will be emailed to participants which will bring them to the quantitative survey. During the disclosure visit, no surveys will be conducted. If the participant does not complete the online survey within two weeks, study staff or data technicians in Geisinger's Survey Research Core will contact the remaining participants to administer quantitative surveys over the telephone. Text message reminders may also be sent to select participants who have agreed to receive Geisinger text message reminders or have agreed to receive PRoGRESS project specific text messages during the consent process. Phone surveys will be conducted using computer-assisted telephone interviewing to ensure completeness and reliability of data. Survey Core data technicians have substantial training in administering surveys to ensure high-quality data and will undergo additional project-specific training. We estimate that the T1 survey will take 30 minutes to complete; T2, T3 and T4 surveys should take 25 minutes to complete.

To more fully understand the lived experience of parents and pediatric participants, we will conduct semi-structured interviews via telephone with up to 45 participants in each of Groups 1 and 2 (i.e., those with a genomic result, 90 participants total). We will not conduct interviews among Group 3 participants, as one key value of the proposed study lies in its focus on understanding the experience of children and families with genomic results. The interviews will be conducted among a sample of Group 1 and 2 participants in Years 1-4. About 15 interviews in each group will be conducted among parents of younger children (ages 0-10) and will, therefore,

not include the child in the interview. Fifteen additional interviews will be conducted with parents of children ages 11-17, with a final 15 interviews being conducted among children ages 11-17. Although some children may only have one parent-participant, we will encourage both parents to participate in a single interview when both parents are participating in the study. Because we recognize that interviewed participants may exhibit heterogeneity in condition type and age of the child, we are prepared to conduct additional interviews as necessary to achieve thematic saturation regarding common experiences as well as to illuminate possible breadth of experiences with this process.

The semi-structured format will allow us to ask all participants about pre-selected constructs for which established measures do not exist (e.g., vulnerable child syndrome, right to an open future) while allowing them to inform us of constructs we might not have considered. Conducting interviews over the first four study years will allow for assessing changes in experience that may be related to changes in practice for the target conditions (e.g., changes in risk management recommendations). Should a participant exhibit clinically significant distress during an interview, the investigator conducting the interview will refer to clinical psychology as detailed in Protection of Human Subjects. Additional qualitative data on the immediate reactions to receiving a result will be gathered in clinical documentation during the disclosure visit by the Genetic Counselor. The visit will be audio recorded for future review. The study team psychologists will work with the Genetic Counselor (who is already trained in psychosocial assessment/counseling) to build metrics for identifying clinically significant distress during the visit.

We will query the electronic health record, assess self-reported risk reduction behaviors, and survey adolescents and parents at 12 months post-disclosure (T4) to determine whether adolescents with a pediatric-onset genomic result have begun disease risk management behaviors.

Using Westlaw Next, the “loss of chance” doctrine as it appears in medical malpractice cases filed in federal and state trial and appellate courts will be examined and monitored, with particular attention to cases involving returning or postponing adult-onset results to children (if any) and reasonably analogous fact patterns. A 50-state survey will be performed, with research focusing on cases filed in the most recent decade in federal and state courts. While medical malpractice is a matter of state law, the forum and venue in which such a case is litigated can be federal, as confirmed by our preliminary research. Standard legal research methodologies will be used to brief cases (e.g., examining the parties, relevant facts, procedural

history, narrow and broad holdings, rules and standards applied, and rationale). Additionally, using Westlaw Next and OpenStates.org and Congress.gov, legislative developments relating to the "loss of chance" doctrine will be explored. Standard legal research methods (including textual analysis, structural analysis, stare decisis and original intent)[45-47] will be used to parse and analyze bills and statutes identified.

4.2 Participant Compensation:

Participants will receive a $25 check or gift card for each completed survey (baseline, T1-T3) and interview. Participants in groups 1-3 who complete a T4 (12 month) survey will receive a $50 check or gift card.

4.3 Data Management Procedures and Confidentiality:

Members of the Geisinger Survey Research Core, study staff (project manager and genomic counseling assistants), and the research data analyst will have access to PHI in the process of administering surveys and extracting data from the EHR, both of which will provide quantitative data. The research data analyst will serve as the study's Data Broker within the Geisinger Phenomics and Clinical Data Core. Survey Research Core staff will use Computer Assisted Telephone Interviewing to collect and record phone survey data directly into the study's database via procedures coordinated by the Data Broker. The Data Broker and project manager will manage all quantitative data, including data extracted from the electronic record and data collected via survey. S/he will be responsible for maintaining the study's quantitative database and for de-identifying any shared data. S/he will maintain a separate electronic file linking study IDs to participants' PHI that can be used to share data with the larger study team. Investigators will not have access to this file linking study ID to PHI.

To enhance Aim 1 by examining how family communication features influence psychosocial and health-related outcomes among parents and adolescents following the disclosure of 1) an adult-onset genetic result, or 2) a pediatric-onset result, Dr. Skye Chernichky-Karcher from Bloomsburg University will help with the design and implementation of the proposed project additions, data analysis, and co-authoring manuscripts from the proposed additions to study Aim 1. Dr. Skye Chernichky-Karcher will receive a limited data set of collected survey data for analysis and reporting of family communication outcomes derived from both parent and adolescent surveys and interviews. To protect confidentiality of the data, Dr. Skye Chernichky-Karcher may access elements of this limited dataset by remoting in to the Geisinger secured network via VPN.

Qualitative interviews will be conducted by the study genomic counseling assistants under the direction of Mr. Buchanan and Drs. Rahm & Mozersky. The genomic counseling assistants will have access to the participants' PHI; Mr. Buchanan and Drs. Rahm and Mozersky will not. Electronic recordings of these interviews will be de-identified before they are sent securely to transcriptionists. The investigators performing the qualitative data analyses from these transcriptions will therefore be unaware of the participants' PHI. The genomic medicine assistants will work with the Data Broker to securely store the electronic file linking IDs from participants who have completed qualitative interviews to their PHI.

Consistent with policies of Geisinger, the Geisinger-Regeneron collaboration, and the clinical genetic testing laboratories that perform clinical confirmation of research generated pathogenic/likely pathogenic results identified through MyCode, CLIA-confirmed genetic results generated through the Geisinger-Regeneron collaboration will be deposited in the ClinVar database. ClinVar has been chosen as a preferred repository for clinically relevant data because Geisinger is a member of the Clinical Genome Resource (ClinGen) grant. Data will be deposited according to the standard deposit schedule of the genetic testing laboratories. Data will be de-identified as set forth in the HHS Regulations for the Protection of Human Subjects and the HIPAA Privacy Rule. Data submission will be consistent, as appropriate, with applicable national, tribal, state laws, and regulations, as well as relevant institutional policies. Our current MyCode consent includes information about sharing of de-identified data for broad research use and is not restrictive as to the specific repositories that might be utilized.

For out of state participants, patient data shared with Genome Medical™ will be protected to the same degree as Geisinger held data via Genome Medical's secure patient portal. As a covered entity, Genome Medical™ has signed an attestation stating that their security controls in place for PHI are equivalent to the controls provided for by the National Institute of Standards and Technology Special Publication 800-53 (rev. 4), medium impact baseline. Geisinger will directly enter the necessary patient data (i.e. patient name, DOB, and contact information) into Genome Medical's secure patient portal only following the participant's written consent after completing the study consenting visit. Geisinger study staff will have access to Genome Medical's patient portal for those out of state study participants to review any data, such as result disclosure information or referrals.

The data generated during the course of this study shall be retained by the Principal Investigator

(PI) for six years as required by Institutional Review Board (IRB) policy. Electronic data will be kept on a password protected computer on Geisinger's secure network. Hard copies of documents will also be retained by the PI for at least six years, and maintained in a locked office.

Data and Safety Monitoring Plan

This study will utilize an Event Monitoring Committee (EMC) to provide independent study oversight focused on the psychosocial wellbeing of pediatric participants. Dr. Bradbury and colleagues have used this specialized version of a Data Safety and Monitoring Board (DSMB) in studies recruiting girls from families with increased breast cancer risk.[1] The EMC improves upon the standard DSMB approach by providing additional oversight for studies in which the greatest potential risks are psychosocial. Dr. Bradbury and colleagues have suggested that EMCs have particular utility in genomic studies with vulnerable populations in which investigators are charged with providing additional protection, as is the case for the pediatric participants in the proposed study. The EMC takes a proactive approach to attempting to prevent adverse events and, if such events occur, rapidly responding to them. The EMC approach seeks to recommend study procedures that minimize risks, analyze anticipated and unanticipated adverse events, and advise study investigators on how to respond to such events if they occur.

For the proposed study, the EMC will be asked to advise investigators on results disclosure and data collection procedures, review and refine protocols for detecting and intervening on clinically significant psychosocial outcomes, review de-identified quantitative and qualitative data for participant burden and psychosocial concerns, review survey data (e.g., anxiety/depression scale scores), and meet with investigators at least quarterly to review study progress and any adverse events. As one of their first tasks, the EMC will also determine the 'stopping rules' for the study (e.g., occurrence of self-injurious behavior or a preponderance of negative psychosocial outcomes in adolescent participants with an adult-onset genomic result). Should a serious adverse event occur, the EMC will be convened within a week to review the event, provide guidance on resolving it, and advise on methods for preventing future events.

Consistent with Dr. Bradbury's experience, we will seek a 5-member EMC with multidisciplinary representation, including an expert in adolescent health, and a biostatistician who can review results from the primary quantitative outcomes as the study progresses.

Adverse events will be monitored by the Project Manager (PM). All study staff and clinicians will be trained to report adverse events to the PM within 72 hours, with serious adverse events reported to the PM and PI within 24 hours. Potential adverse events for this project include

adverse psychological outcomes (e.g., distress), up to and including self-injurious behaviors. Any adverse events that occur during a genomic medicine consultation will be managed clinically as per the clinical psychologist-led protocol described below under Expected Risks. The study's clinical psychologists will also manage adverse events that occur during quantitative or qualitative data collection as described below under Expected Risks. If the genetic counselor notes the need for referral to mental health services while conducting a follow-up call with a participant, the counselor will enact the protocol described below under Expected Risks. With input from the Survey Research Core staff, clinical psychologists and genetic counselor, we will actively track and respond to all adverse events and protocol deviations. Once data collection begins, investigators, the PM, and Data Broker will meet at least monthly to discuss project implementation, address questions or concerns that might arise, and monitor the safety of the data collection. The PM will record, review and discuss any deviations or adverse events that have occurred since the last meeting. Adverse event forms will be used to report all unanticipated events. The report will include date, description and outcome of the event. Unanticipated adverse events will be reported within 7 days to the Geisinger IRB, study EMC, and to NHGRI. A written follow-up will be submitted within 30 calendar days. All adverse events (serious or not, related or unrelated, anticipated or unanticipated) will be reported in regular reporting to the EMC and NHGRI.

The Data Broker will maintain security of the study database and file linking study IDs to PHI by storing them behind the Geisinger firewall and password encrypting these files. The servers on which study data will be kept are in a secure computer room and are backed up daily.

All individuals involved in data collection and clinical care will be trained to document and report any deviations from the protocol, adverse events, or unusual responses immediately to the PM and PI. The PM, PI, and biostatisticians will monitor data collection procedures on a regular basis for quality assurance purposes.

4.4 Data Analysis/ Statistical Considerations:

For psychosocial outcomes in Aim 1, we have specified a priori each pairwise comparison to be of interest. Therefore, all calculations assume 80% power and 5% significance level. Assuming a 10% dropout and a minimum detectable effect size (change in standard deviation units) for the key quantitative psychosocial outcomes is 0.4 for each of the comparison of Group 1 vs. Group 2, Group 1 vs. Group 3, and Group 2 vs. Group 3, we will need a sample size of at least 447 participants (112 parents and 37 adolescents in each group). If we are successful in recruiting a

second parent for some of the minors, then we can expect the minimum detectable difference to decrease. This effect size is considered moderate in size and is less than the effect size seen in a previous study that used the Hospital Anxiety and Depression scale in a sample of adolescent girls from families with *BRCA1/2* variants[5].

We anticipate that there will be a sufficient sample population to achieve the enrollment goal of 447 participants (336 adults and 111 adolescents). As of 8/1/2020, 1,582 MyCode participants have received a pathogenic/likely pathogenic variant in a gene on the MyCode gene list. Excluding autosomal recessive conditions (hereditary hemochromatosis, MUTYH-associated polyposis) leaves 1,379 probands we could approach to determine whether they have minor relatives who have not been tested for the familial variant. Based on a review of the family histories of 100 of these individuals and accounting for 10% of probands being deceased and 10% of relatives having had cascade testing, we estimate that there will be approximately 1,525 minor first- and second-degree relatives who have not had cascade testing. To reach the enrollment goal, we would need to enroll 22% of available parents and adolescents (336/1,525 and 112/508, respectively). This recruitment rate seems feasible based on the experience of other studies on MyCode participants and their families. Note, too, that the sample population will continue to rise through 2021 as several hundred more MyCode probands receive a pathogenic/likely pathogenic variant in a gene on the MyCode list.

5.0 Table 3. EXPECTED RISKS:

Proposed Harm	Protection Plan
Psychological harms • Negative impact on self-esteem/bodyimage • Stigmatization • Increased anxiety • Distress • Development/worsening of depression	Assess self-esteem, body image, anxiety, distress and depression in quantitativesurveys Survey research staff trained to notify pediatric clinical psychologist of clinically relevant scale scores Qualitative researchers notify pediatric clinical psychologist of psychological concerns that arise during qualitativeinterviews Pediatric clinical psychologist intervenes therapeutically when scale scores are clinically significant or qualitative interviewers note psychological concerns

	□ Pediatric clinical psychologist assesses these psychological constructs during regular sessions and intervenes therapeutically per usual clinical practice

Negative effect on family • Negative impact on familyrelationships • Distortion of parental impression ofchild's capacity (vulnerable child syndrome)	□ □ Assess family functioning and cohesion in quantitative surveys Survey research staff trained to notify study psychologists of scale scores that indicate family is at risk of dysfunction □ Qualitative researchers notify clinical psychologists of family functioning concerns that arise during qualitative interviews □ Psychologists and social worker leadfamily therapy sessions for families at risk of dysfunction □ Pediatric clinical psychologist assesses child's perceptions of family functioning during regular sessions and intervenes therapeutically per usual clinical practice

Social discrimination and restrictions • Insurance discrimination • Social discrimination by peers • Employment discrimination • Educational discrimination • Restricted life choices	Insurance and employment discrimination prohibited by Genetic Information Nondiscrimination Act of 2008 Pediatric clinical psychologist will assess child's perceptions of school performance/treatment during regular sessions and intervene therapeutically per usual clinical practice Informed consent and assent process notes the potential risk of restricted life choices; family cannot participate unless child assents
Autonomy • Failure to respect future autonomy • Breach of confidentiality due to results disclosure to parents • Risk of child misunderstanding information	Informed consent and assent process notes the potential risks to autonomy and confidentiality; family cannot participate unless child assents Risk of misunderstanding of information minimized by having a genetic counselor experienced with pediatric cancer genetics disclose results to all assenting pediatric participants

6.0 EXPECTED BENEFITS:

The study will assess psychosocial outcomes among pediatric participants who do and do not receive a genomic result. It will also assess psychological and behavioral outcomes among their parents. It is possible that the relatives of participants in Group 1 (adult-onset result) will benefit by detecting a previously undetected genetic risk that prompts them to initiate performance of behaviors known to greatly reduce cancer or cardiovascular disease risk. As noted above, such risk reduction in parents could also directly benefit their children by preventing illness in the children's caretakers. Additional theoretical benefits to pediatric Group 1 participants include preparing for the future, positively incorporating the results into their self- image, adopting healthy behaviors, and preventing a missed opportunity to report their results to them once they reach the age of majority. Pediatric and adult relatives of Group 2 participants may also benefit from using this genomic information to reduce their morbidity and mortality. Group 3

participants might benefit by learning that genetic testing found that they do not carry the familial pathogenic variant. More broadly, study outcomes will inform best practices for incorporating genomic information into the care of pediatric patients and their families. Given these anticipated benefits, the risks of participation described above are reasonable.

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