Protocol

# Increasing Germline Genetic Testing for Patients with Cancer (gLHS)

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# Increasing Germline Genetic Testing for Patients with Cancer

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## Study Schema

# 1. Protocol Summary

Germline testing for hereditary cancer syndromes is underutilized across most health care settings. Using a learning health care approach, the Genomics-enabled Learning Health Systems (gLHS) network aims to evaluate the impact of a suite of implementation strategies to increase germline test ordering by oncology care teams for eligible breast, pancreatic and colorectal cancer patients (i.e., mainstreaming). Secondarily, we will investigate completion of testing by eligible patients, as well as impact on overall rates of germline test ordering in cancer patients. The network will bundle and deploy different implementation strategies across the clinical sites in three approximate 6-month phases. A maintenance phase after the implementation periods will measure genetic testing rates without any additional implementation strategies to determine persistence of effects. The implementation strategies address clinician-level factors, and thus oncologists and their team members (e.g. advanced practice providers, nurse navigators, case managers) will be the focus of evaluation for impact of implementation strategies. Strategies that will be considered include provider education, audit and feedback reports, facilitation, peer support, and electronic health record (EHR) system optimization to support germline testing. Using the RE-AIM QuEST framework, outcomes will be assessed using mixed methods separately for each eligible cancer type. Data collection from the EHR, other relevant data sources, and qualitative provider feedback, will be used to assess ordering and completion of tests and the effect of the implementation strategies on germline testing rates in oncology clinics.

# 2. Background

## 2.1 Description of Network

The translation of genomic discovery to clinical practice has yet to reach its full potential in guiding health care and improving health outcomes for all populations. Multi-level barriers include: a limited scope of previous implementation efforts to a small set of health conditions, lagging payor reimbursement and coverage policies, lack of interoperability of genomic data, limited clinician familiarity with genetic testing, demonstration of clinical utility limited to prevalent genetic diagnoses, and non-scalable approaches to returning genetic data to the medical record. To address these issues, the Genomics-enabled Learning Health System (gLHS) network was created to facilitate adoption and implementation of evidence-based genomic medicine practices across varied health systems and clinical settings. Funded by the National Institutes of Health (NIH) in September 2024, the network is composed of 6 clinical sites, 9 community partners, and a coordinating center (CC). The aim of the gLHS network is to identify and improve clinical integration of genomic medicine through a learning health system cycle of implementation, assessment, refinement, and re-implementation. As described in the National Human Genome Research Institute (NHGRI) strategic plan (**Figure 1**)[1] the network will use a combination of efforts such as quality improvement and implementation science to improve routine care. Harnessing team science approaches, the network will develop and implement genomic implementation projects across the network deployed through multiple implementation cycles with outcome measurements. During the first 3 months, the network developed a framework focused on clinical utility and implementation gaps, financial implications, health care access, impact, equitable reach, and feasibility to weigh the strengths of potential implementation projects. Three

action groups drive the network. These groups focus on implementation science, clinical science and health systems, and EHR tools.

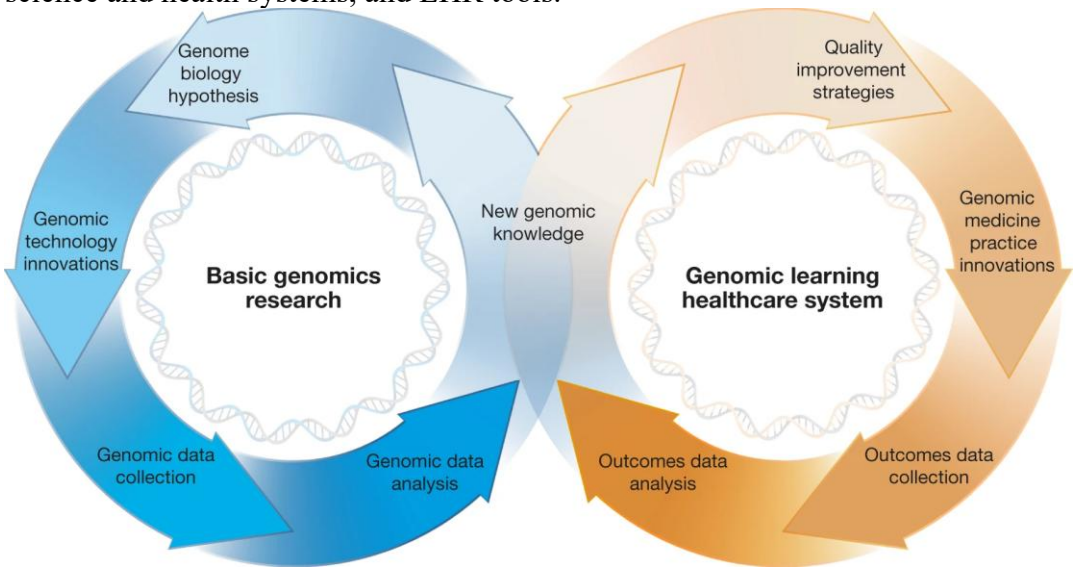


**Figure 1**: Genomic learning health system from the National Human Genome Research Institute (NHGRI) Strategic Plan of 2020

**2.2 Implementation Study to Improve Genetic Testing of Cancer Patients**

This project seeks to close the acknowledged care gap in genetic testing of hereditary cancer predisposition by evaluating implementation strategies expected to increase guideline-concordant germline genetic testing (referred to in protocol as "germline testing" and defined as testing of inherited gene variants related to cancer) by oncology care teams (i.e., 'mainstreaming', or 'task-shifting' from the traditional genetic consultation referral model). Identification of hereditary risk is critical for individuals with a cancer diagnosis, as it can have implications for treatment, with targeted therapies. Furthermore, identifying individuals with hereditary risk provides an opportunity for surveillance for early detection of other cancers or risk-reducing procedures. Knowing a pathogenic variant also allows for cascade testing in family members.

Germline testing for hereditary cancer within current clinical practice is underutilized across most health care settings, even when evidence supports effectiveness to inform clinical care. Inadequate testing has led to low detection rates of individuals with hereditary cancer syndromes, especially among different groups[2–4]. Mainstreaming is an alternative service delivery model that has emerged to improve access to germline testing [5–7]. It shifts the clinical activities of pre- and post- test processes of germline testing to frontline clinician teams. **Figure 2** below from Mackley et al. (2025)[7] demonstrates the various mainstream models depending upon the involvement of the geneticist or non-geneticist in the germline testing process. Here, we will be studying the implementation of mainstreaming throughout the germline testing process, from recognizing patients who are eligible for germline testing to disclosing results for those who opt to test.

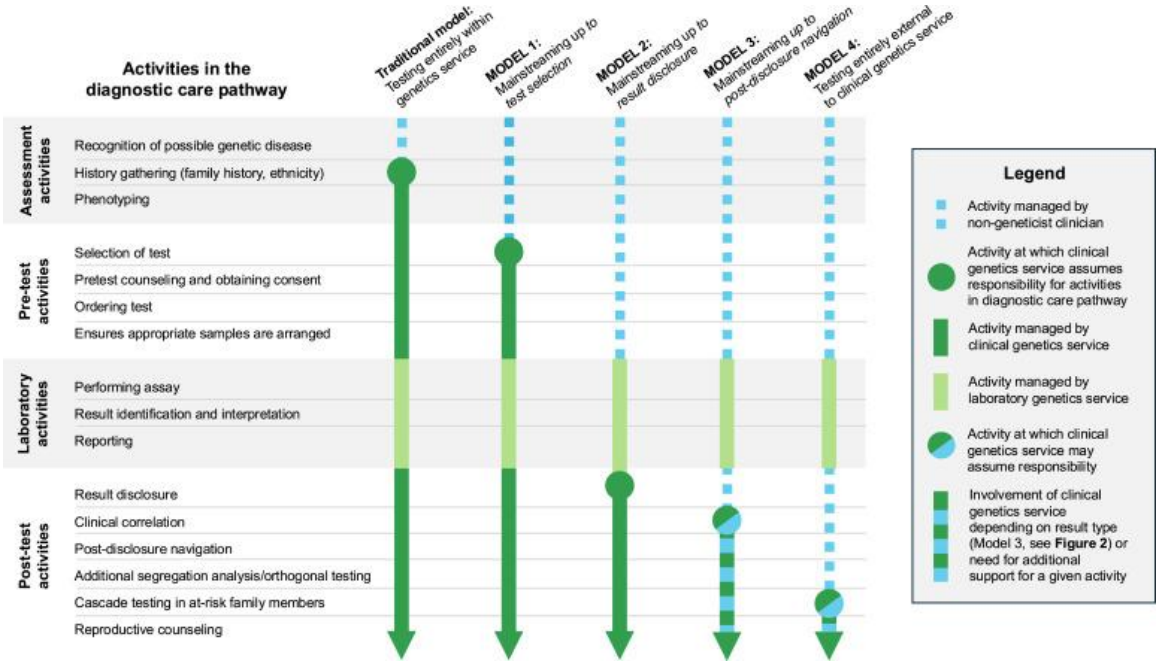


**Figure 2:** Activities in the diagnostic care pathway and whether they are managed by the genetic services (green) or nongenetic clinicians (blue) in different models of care.

We will assess changes in germline test orders for and completion by patients with cancer who receive care across the clinical sites in the gLHS network before and after deploying implementation strategies designed to promote testing uptake. There will be three implementation phases followed by a maintenance period **(Figure 3).** The selected implementation strategies are widely used to improve clinical practice and address previously reported barriers in the literature[8–11]. These strategies will aim to increase mainstreaming of germline testing by oncology teams.

Most studies evaluating mainstreaming of germline testing for cancer have been performed in relatively small numbers of patients often at single institutions focusing on outcomes of feasibility and patient and provider satisfaction[12–15]. Implementation outcomes (e.g., reach, adoption, implementation) precede and impact both service and patient outcomes[16]. Thus, understanding implementation outcomes for mainstreaming of germline testing, as well as contextual factors that are associated with successful implementation, is fundamental to achieving high-quality genetic health care. Definitions of common terminology used throughout the protocol can be found in **Table 1.**

**Table 1.** Protocol definitions.

| Term | Definition |
|---|---|
| Provider | The clinician in charge of ordering genetic testing; also this population is evaluated as participants in this study. |
| Oncology care team | The team of individuals associated with patient care that can place orders for germline testing, such as but not limited to advanced practice providers, nurse navigators, case managers, and/or surgeons. |
| Patient | Individuals seen by the providers that have been diagnosed with colorectal cancer diagnosed under age 50, female breast cancer diagnosed under age 66, or pancreatic cancer diagnosed at any age. |
| Data extraction | Collection of relevant data elements needed for outcomes analysis, can be pulled from sources such as but not limited to the electronic medical record (EHR), testing companies, and discussions with providers. |
| Germline testing | The testing of germline DNA variants associated with hereditary cancer predisposition. |
| Mainstreaming | An alternative health care model that shifts the clinical activities of pre- and post-test processes of germline testing to frontline clinician teams, instead of utilizing referrals to genetic counselors. |
| CFIR 2.0 | Consolidated Framework for Implementation Research version 2.0 |
| RE-AIM QuEST | A mixed-methods approach designed to evaluate public health programs and interventions comprehensively, blending quantitative and qualitative data to assess key program dimensions. It evaluates programs across five domains: Reach, Effectiveness, Adoption, Implementation, and Maintenance. |
| Implementation Strategy | Methods and tools used to enhance the adoption, implementation, and sustainability of a clinical practice or intervention |
| Intervention | Program or practice being implemented; in this protocol, mainstreaming |
| Determinants | Characteristics of a delivery context that act as barriers or facilitators to the successful uptake of an intervention |

## 3. Rationale, Aims, and Hypotheses

**Aim 1**: To evaluate the impact of implementation strategies deployed over three phases on (a) germline test ordering for eligible breast, pancreatic and colorectal cancer patients by oncology care teams (primary outcome) and (b) completion of orders by eligible patients (secondary outcome).

H1: *Guideline-concordant germline test ordering by oncology care teams for eligible breast, pancreatic, and colorectal cancer patients will increase after implementation strategies are deployed compared to baseline.*

H2: *Guideline-concordant germline test completion by eligible patients will increase after implementation strategies are deployed compared to baseline.*

**Aim 2**: To understand multi-level barriers and facilitators to increasing guideline-concordant germline genetic test ordering by oncology care teams and completion by eligible breast, pancreatic and colorectal cancer patients.

*Rationale: Understanding the determinants of germline testing by oncology care teams will enable modifications and adaptations to implementation, leading to improved implementation of test order and improved test completion in patients.*

# 4. Study Design

## 4.1 Overview

This implementation study will assess the effect of different implementation strategies on increasing guideline-concordant germline testing by oncology care teams caring for patients with specific cancers (**Figure 3**). As detailed below, we will deploy different implementation strategies across the clinical sites in three approximate 6-month phases. An approximate 12 to 24-month maintenance phase will measure genetic testing rates without any additional implementation strategies to determine persistence of any effect. Phases and maintenance periods may be shorter or longer due to site specific factors with regards to implementation. Implementation strategies may also need to be adjusted across phases depending on current site-specific requirements and current practices.

The baseline, serial intervention, and maintenance phases will be analyzed using an interrupted time series (ITS) design. There will be no randomization at the patient, clinician, or clinic levels.

## 4.2 Intervention description

The clinical intervention we will study is mainstreaming of germline testing by oncology care teams for adult patients with colorectal cancer diagnosed under age 50[17], female breast cancer diagnosed under age 66[18], and pancreatic cancer diagnosed at any age[19]. These cancer diagnoses and age ranges follow evidence-based guidelines describing indications for germline testing for these patients (e.g., the National Comprehensive Cancer Network, American Society of Clinical Oncology-Society of Surgical Oncology).

## 4.3 Implementation Strategies

As shown in **Figure 3**, we anticipate three implementation phases, introduced approximately 6 months apart, followed by an approximate 12 to 24-month maintenance phase where no additional implementation strategies are introduced. Implementation bundles will be flexible allowing sites to adapt certain features to their specific setting. For example, if a site has already implemented a component of a bundle they can further optimize or enhance their current strategy to align with project goals. Furthermore, sites will be able to identify the elements of each phase that are most appropriate for local implementation, e.g., through local governance processes. All existing strategies and changes to those strategies will be documented (described in ‘outcomes’ under ‘fidelity’) using established implementation science approaches. Ongoing implementation strategies from prior phases (e.g., audit and feedback) will continue into future phases, as appropriate and deemed to continue to be useful at sites.

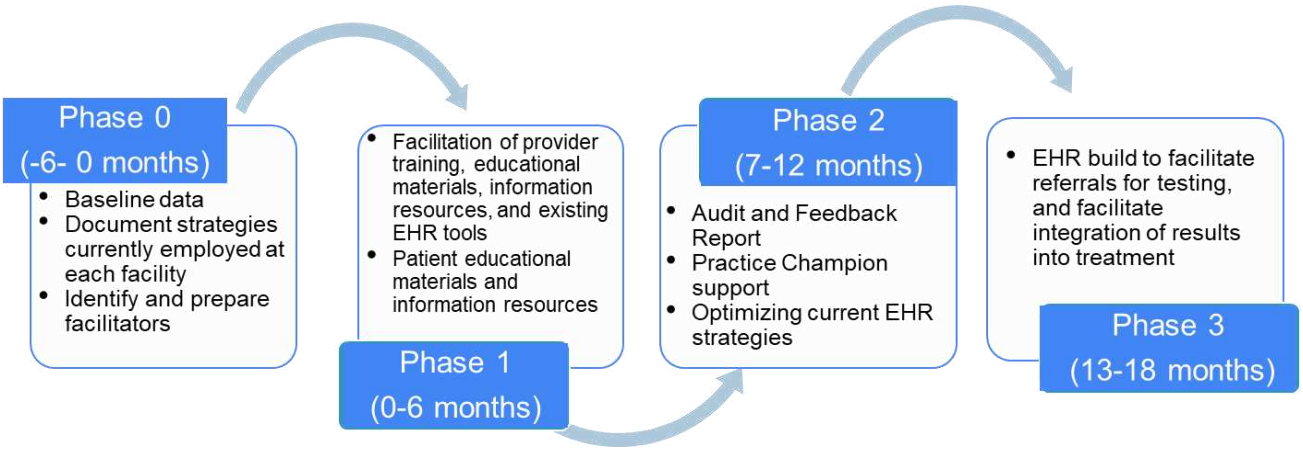


**Figure 3**: Three phases of implementation strategy bundles will be deployed during the study. The items in each phase are representative elements anticipated to be considered for inclusion by each clinical site in each phase.

Implementation strategies and phases are described below. The inclusion of an implementation approach means that the approach will be considered for implementation at each site. Whether the specific approach, or any of its component elements, is implemented at the site will depend on factors such as whether the site already has implemented it, or whether it is feasible to implement and approved by relevant governance bodies as appropriate

Prior to facilitation of the implementation strategies the network will identify local champions for mainstreaming by oncology care teams. Champion(s) will be considered internal facilitators.

The first implementation phase primarily addresses highly ranked and mutable determinants related to 1) patients' interest in and motivation for testing as well as their privacy concerns, and 2) provider's knowledge of which patients are eligible for testing and how to order tests. This phase will focus on strategies that do not necessarily require changes to the EHR and the implementation strategies will be adjusted at each site based on resources, workflows, and whether and how much components of the strategies may already be in place.

Implementation strategies in this phase that address those determinants may include:
1) **Facilitation of provider training, educational materials, and information resources,** including on the use of existing EHR tools. Provider outreach and training will focus on identification of patients eligible for testing, consent in a clinical setting for germline testing, and workflow templates describing how to place a germline testing order at their site. Provider education to increase awareness of existing EHR tools will be included as well.

2) **Patient-facing educational material and information resources.** Resources will be available to providers at each site to support them in educating patients about germline testing. Online and printed materials will be made available to providers to address

general information about genetic testing, insurance coverage, and privacy concerns. Resources will be pulled from existing published materials and made available to providers to use at their discretion. No new educational resources will be produced for this gLHS project implementation. Providers can also use existing materials from their institutions as part of routine clinical practice. Examples of online published materials include those from Facing Our Risk (FORCE; facingourrisk.org) specifically the GINA, colorectal cancer, pancreatic cancer, and breast cancer patient education materials.

The second implementation phase primarily addresses highly ranked and mutable determinants related to providers' willingness to order genetic tests, comfort with obtaining patient consent in the clinic for genetic testing and results disclosure, and knowledge of which patients are eligible for testing. For EHR optimization, this phase will focus on strategies that require moderate effort to implement, i.e., can be approved and implemented by the start of Phase 2 of the implementation.

Implementation strategies in this phase that address those determinants may include:
1) **Audit and feedback report on existing patients.** Sites will provide oncology care teams audit and feedback reports. These reports will include elements such as data about historical germline testing rates, by individual provider, clinic, and institution, lists of eligible cancer patients who have not had tests ordered and comparator data may also be provided. Reports will be delivered electronically, through one-on-one communication, or team meetings and discussions.

2) **Practice champion support.** Peer support can include expert consultation and discussions between the champions, clinic leaders, providers, and staff. Expert consultation (e.g., webinars and technical assistance as needed), peer-to-peer calls, during which clinics can share their experiences, and onsite and/or virtual visits to engage with leaders, clinicians, and staff to discuss progress and share audit and feedback information may also be implemented as needed at each site.

3) **Optimizing EHR strategies.** Improvements to deployment or content of existing EHR strategies will be included in this phase. These include elements such as increase in awareness of existing EHR tools within clinical site and improved deployment and improved content or format of existing EHR tools.

The third implementation phase primarily addresses highly ranked and mutable determinants related to identifying patients who meet clinical criteria for genetic testing (which can be time intensive and require addressing the challenge of finding prior genetic testing records) and navigating complexity of genetics workflows and sample tracking. For EHR optimization, this phase will include strategies that may require significant effort to implement, i.e., may be difficult to approve and implement by the start of Phase 2, but can be approved and implemented by the start of Phase 3 of the implementation.

Implementation strategies in this phase that address those determinants may include
1) **EHR tools to facilitate prospective identification of patients, testing, and result reporting**. Our implementation approaches will make use of the EHR as well as other

available data sources, if appropriate (e.g., genetic testing data obtained from genetic testing laboratory vendors, use of artificial intelligence (AI) approaches to extract structured data from unstructured data sources). All strategies will be developed and delivered in a secure, HIPAA-compliant manner and are typical clinical improvement practices incorporated within routine clinical care.

As the network develops the resources and tools needed for each of the implementation strategy bundles, existing tools, resources, best practices, and other key elements to ensure the success and efficiency of this project will be shared across sites. All deployments will have approval from relevant governance groups and leadership at the clinical sites, such as medical directors and EHR operations committees.

# 5. Implementation Framework(s)

### 5.1: Strategy Identification Framework: CFIR

To develop our strategies, we employed the Consolidated Framework for Implementation Research (CFIR) 2.0 to identify determinants that are both important and mutable. Determinants were matched with implementation strategies using the CFIR-ERIC strategy matching tool and consensus among clinical sites **(Table 2)**[8–11]**.**

### 5.2: Implementation Outcomes Framework: REAIM QuEST

We will employ the RE-AIM QuEST framework to evaluate the impact of strategies on our outcomes of interest[20]. The RE-AIM QuEST framework is a mixed-methods approach designed to evaluate public health programs and interventions comprehensively, blending quantitative and qualitative data to assess key program dimensions. It builds on the widely used RE-AIM framework, which evaluates programs across five domains: Reach, Effectiveness, Adoption, Implementation, and Maintenance. RE-AIM QuEST enhances this framework by incorporating qualitative methods to better understand contextual factors and mechanisms underlying program outcomes.

**Table 2:** Site reports of CFIR determinants

| Level | Determinant |
|---|---|
| **Patient** | Insurance coverage |
| | Privacy concerns |
| | Interest/Motivation |
| | Care priorities |
| **Clinician Level** | Knowledge of what patients are eligible for genetic testing |
| | Knowledge of how to order genetic testing (using EHR and/or lab portal) |
| | Identifying eligible patients can be time intensive |
| | Confidence in obtaining clinical genetic testing consent given time and complexity |

| | |
|---|---|
| | Willingness to order genetic testing as part of scope of practice |
| | Documentation of genetic testing consent is complex |
| | Comfort with results disclosure |
| | Knowledge of which test is to be ordered |
| **System level** | Prior genetic testing records are difficult to find |
| | Complex workflow |
| | Sample tracking complexity |

# 6. Study Population and Setting

The target population for this study includes clinician members of oncology teams who care for adults with breast, colorectal, or pancreatic cancer. We will evaluate implementation strategies promoting the ordering of appropriate germline testing for these patients by the oncology teams. These strategies will target physicians and advanced practice providers (nurse practitioners and physician assistants/associates) practicing at the target clinic types. Further details about the clinical sites and targeted clinics and providers are provided below.

# 7. Study Sites and Enrollment

## Study Enrollment Locations

Oncology care teams caring for adult patients with breast, colorectal and pancreatic cancer. Site specific information is described below.

**Geisinger**

Geisinger is a fully integrated health system that includes 10 hospital campuses, a health plan with more than half a million members, and our College of Health Sciences, which includes the Clinical Education Institute, Research Institute, the Geisinger Commonwealth School of Medicine (GCSOM), and the Geisinger School of Nursing. Geisinger serves more than 1 million patients in Pennsylvania and is a physician-led organization with over 26,000 employees. Geisinger is centered around a cutting-edge multispecialty group practice of more than 1,700 physicians who practice at 133 primary care and specialty clinics throughout the region. Geisinger outpatient facilities see approximately 2.6 million clinic visits annually. For this study, a total of 48 clinicians (25 physicians, 15 nurse practitioners, 8 physician assistants/associates) across 11 outpatient Geisinger medical oncology clinics in central and northeastern Pennsylvania could be engaged in participation. All clinicians identified have seen at least 10 patients with relevant cancer diagnosed in the past two years.

**Indiana University**

Indiana University Health (IUH) is the largest and most comprehensive healthcare system in Indiana. It is comprised of 16 hospitals and over 38,000 employees. There are over 100,000 admissions and more than 1.2 million unique patients treated. IUH offers a full range of specialty services and the partnership with IUSM allows access to research,

clinical trials, and destination services. The Indiana University Simon Comprehensive Cancer Center records >40,000 outpatient visits per year. The Indiana Familial Cancer Clinic began in 1993 to provide care to families with a history of cancer. Clinical geneticists and cancer genetic counselors in the Department of Medical and Molecular Genetics provide genetics evaluation, genetic counseling, risk assessment, genetic testing and medical management services to individuals with a personal and or family history of cancer, polyps or pancreatitis. The clinic also provides services to children and adults with a gene mutation known to be causative for an increased cancer risk. IUH has >30 licensed genetic counselors, and the IU School of Medicine has an additional 9 genetic counselors in a research or education capacity.

IUH provides comprehensive care for cancer patients in clinics across the state of Indiana. Over the last 5 years, there were at least 32 clinicians who are oncology specialists who saw at least 100 breast cancer patients; these were 17 clinics across Indiana. There were at least 48 ordering prescribers who provided care for at least 50 pancreatic cancer patients; these were in 14 oncology clinics across Indiana. There were 18 ordering prescribers who provided care for at least 30 colorectal cancer patients; these were in 8 oncology clinics across Indiana. In the year April 2024-March 2025, there were 1,895 unique breast cancer patients, 634 unique pancreatic cancer patients, and 1,747 unique colorectal cancer patients who did not have a ICD10 diagnosis code for these cancers before April 2024.

**Northwestern University**
Northwestern Medicine is a nonprofit, integrated academic health system anchored by its flagship, Northwestern Memorial Hospital in downtown Chicago. The Northwestern Memorial Healthcare (NMHC) System has expanded through a series of strategic affiliations, growing to encompass 11 hospitals and over 200 care locations across Illinois. The network includes Northwestern Memorial Hospital, a Magnet-designated, 894-bed academic medical center and teaching hospital affiliated with Northwestern University's Feinberg School of Medicine. Northwestern Memorial is consistently ranked #1 in Chicago and Illinois, and among the top 10 hospitals nationally in multiple specialties. The system also includes Prentice Women's Hospital, a specialized 256-bed facility offering advanced obstetric, gynecologic, and neonatal care, including a Level III NICU, as well as hospitals in Lake Forest, Central DuPage, Delnor, Marianjoy Rehabilitation, McHenry, Woodstock, Kishwaukee, Valley West, and Huntley, serving suburban populations with comprehensive inpatient and outpatient services.

NMHC employs over 5,000 physicians and 40,000 staff, and benefits from its close partnership with the Feinberg School of Medicine, seamlessly blending patient care, education, and cutting-edge research, including more than 4,500 clinical trials annually. NMHC serves more than 1.2 million patients per year. Northwestern Memorial Hospital (NMH), the academic flagship of this system, is one of the country's premier academic hospitals and a national and international referral center. For the past seven years NMH has been recognized by U.S. News & World Report as an "Honor Roll" hospital, and in 2021 U.S. News ranked NMH 10th in the United States. NMH also houses the NUCATS Clinical Research Unit, a developmental therapeutics program, and actively enrolls patients in every clinical department of the hospital. Clinical research studies at NMHC

have more than doubled in the past decade, as the health system has established growth of its research enterprise as one of three strategic pillars.

The Northwestern Medicine Oncology program provides comprehensive cancer care from diagnosis, through treatment and survivorship. Over 100 clinicians provide breast, pancreas, and colon cancer care across 38 clinical sites in the NM system. Between 2023-2025, the mean number of new breast CA patients evaluated monthly was 403, pancreas - 154, and colorectal - 68. While a mean of 21 breast CA patients was evaluated each month per site, the actual patient volume varies widely by site ($25^{th}$ percentile = 3 patients/month; $75^{th}$ percentile= 31/month). Similarly, pancreatic CA was treated by 101 clinicians at 38 sites with a mean of 6 patients per month per site ($25^{th}$ percentile = 1.4; $75^{th}$ percentile= 7.6); colorectal CA was treated by 89 clinicians at 36 sites with a mean of 3 patients per month per site (25th percentile = 1.5; 75th percentile = 3).

**University of Miami**
UHealth (University of Miami Health System) is South Florida's only university-based medical system and consists of over 2,700 providers and scientists who provide state-of-the-art medical care. UHealth provides care in over 100 medical specialties. UHealth is rated among the best hospitals in Florida across 15 areas of medical care by *U.S. News & World Report* Best Hospitals 2025-26, with the Bascom Palmer Eye Institute, Neurology & Neurosurgery, and Sylvester Comprehensive Cancer Center nationally ranked. The UHealth system also includes nearly 40 outpatient locations in Miami-Dade, Broward, Palm Beach, and Collier counties, including The Lennar Foundation Medical Center. UHealth's Sylvester Comprehensive Cancer Center is the only NCI-designated cancer center in South Florida and is ranked among the nation's top 50 for cancer care. Sylvester Comprehensive Cancer Center consists of multiple locations across Miami-Dade and Broward Counties. In 2024, over 600 physicians provided care to over 50,000 patients at Sylvester Comprehensive Care Center. Sylvester Comprehensive Cancer Center cares for international patients from 84 countries, including the Bahamas, Ecuador, Trinidad and Tobago, and Venezuela. The University of Miami is a community partner of the VUMC clinical site.

**University of Utah**
University of Utah Health (UU Health) is the only academic medical center in the state of Utah and the Mountain West and provides patient care for the people of Utah, Idaho, Wyoming, Montana, western Colorado, and much of Nevada. It also serves as the training ground for the majority of the state's physicians, nurses, pharmacists, therapists, and other health care professionals. Staffed by more than 20,000 employees, UU Health is recognized nationally as a transformative healthcare system and regionally as a provider of world-class care. For 15 consecutive years, UU Health has been ranked among the top 10 academic medical centers nationally in terms of quality, safety, and accountability by Vizient, Inc. In 2024, it was ranked #3 in the nation for ambulatory care in terms of access to care, quality, efficiency, continuum of care, and equity.

UU Health includes five hospitals, 12 community healthcare centers, 22 regional partners and 75 telehealth sites; and several specialty centers including the Huntsman Cancer

Institute, John A. Moran Eye Center, the Cardiovascular Center, the Clinical Neurosciences Center, and the Utah Diabetes & Endocrinology Center. Collectively, UU Health has approximately 680 inpatient beds and provides care for 2 million Utahns and residents of five surrounding states in a referral area encompassing more than 10% of the continental United States. UU Health is staffed by over 1,600+ board-certified physicians representing 200 medical specialties, 8,000 committed staff members, and over 700 full-time registered nurses.

For the targeted cancers, there are four main oncology clinics where medical oncologists see patients for these cancers. These are located both at the Huntsman Cancer Institute in Salt Lake City, Utah and in outlying locations including the Sugar House Health Center, the Farmington Health Center, and the South Jordan Health Center.

**Vanderbilt University Medical Center (VUMC):** Vanderbilt Health, housed at Vanderbilt University Medical Center in Nashville, Tennessee, is one of the largest and most prominent academic systems in the Southeast. With 43,000 employees in its workforce, VUMC provides patient care, conducts research, and trains future health professionals. Vanderbilt University Medical Center is comprised of 7 hospitals and 180+ clinic locations across middle Tennessee. The health system provides 3.3 million patient visits annually. Vanderbilt-Ingram Cancer Center (VICC) is an NCI-designated Comprehensive Cancer Center and a member of the National Comprehensive Cancer Network. VICC cares for more than 7,000 new cancer patients each year. VICC's team of more than 200 physicians conducts more than 180,000 outpatient visits each year.

**Department of Veterans Affairs (VA):** The Veterans Health Administration is the largest integrated health care system in the United States, providing care at >1300 health care facilities, including >170 VA Medical Centers and >1,100 outpatient sites of care of varying complexity. VA facilities are located in all 50 states, the District of Columbia, the Philippines, and the US territories (Puerto Rico, US Virgin Islands, Northern Mariana Islands, Guam, and American Samoa). The VA serves 9.4 million Veterans enrolled in the VA health care program, which covers eligible Veterans who meet certain criteria based on their service history, disability status, income level, and other factors.

# 8. Alterations to Consent Process

## 8.1 Overview

In this study, we are examining how provider-focused strategies affect their actions with regards to ordering germline testing of patients with cancer. As clinical genetic testing is considered standard for the patient populations cared for by the study providers, clinical guideline-based care is not an investigative procedure. Providers will obtain and document clinical consent for germline genetic testing as per local routine clinical practice. **Table 3** summarizes the requested alterations to the consent process.

We are requesting a waiver of informed consent for the providers related to the implementation strategies initiated and delivered by study personnel. The rationale for the waiver is that the research is minimal risk (section 8.2), preserves provider autonomy (section 8.3), and is impractical to conduct without a waiver (section 8.4). The research is

not greater than minimal risk as it utilizes different implementation strategies focused on the provider that the provider can decide to act upon or not. The provider autonomy is preserved in that the decision of whether to order germline testing or not is determined solely by the provider for each patient. Additionally, requiring formal informed consent for the providers and their care teams may create a bit of a Hawthorne Effect where providers alter their behavior with regards to germline test ordering and compromise the ability to understand the impact of the implementation strategies on provider behavior. Furthermore, only including providers who were amenable to the implementation strategies would likely overestimate the uptake of the strategies and germline mutation test ordering as the most receptive providers would be the ones to consent, while unreceptive providers might not consent and their testing practice would not be included in the study results. This would bias the results and not give an unbiased assessment of the effect of instituting these implementation strategies widely on germline testing rates for these cancers.

Secondly, we are requesting a waiver of documentation of informed consent for the providers and oncology care team members who agree to be interviewed. These procedures are minimal risk, preserve provider anonymity, and do not involve procedures where informed consent is required outside of the research context. Provider interviewees will be informed about the study purpose, procedures, risks, benefits, and voluntary nature of participation through an oral consent script provided at the start of the interview and prior to asking any research questions. The providers and/or oncology care team members will be given the opportunity to ask questions and explicitly agree to proceed before the interview begins.

Finally, we request a waiver of consent for data extraction of patient records to inform implementation outcomes, as the study is minimal risk, preserves autonomy of patients, and the study does not directly interface with patients. The patients will be consented for the genetic testing as part of routine clinical care. The research would simply involve collecting data on patient testing and outcomes that is already available in the medical record. Conducting this research without a waiver of informed consent to collect patient records would be otherwise impracticable and only including patients who are willing to consent would bias the results toward patients who are also agreeable to the genetic testing.

**Table 3:** Summary of requested alteration of consents.

| Study population | Study intervention | Alteration of consent |
|---|---|---|
| Clinicians | Implementation strategies in Figure 3 in section 4.3 | Waiver of informed consent |
| A subset of clinicians invited for interviews. | Interviews | Waiver of documentation of informed consent |
| Patients | Data extraction of EHR and genomic results data for outcomes analysis | Waiver of informed consent |

## 8.2 Study procedures are minimal risk to patients and providers

The project is designed to pose minimal risk to both patients and providers, as defined by regulatory standards. Specifically:

- **Nature of the Intervention**: The project involves the implementation of health informatics tools such as clinical decision support (CDS) tools, workflow optimization, and educational resources to increase guideline-indicated germline testing for hereditary cancer syndromes. These interventions are integrated into routine clinical care, presenting no additional physical, psychological, or financial risks.
- **Data Collection**: The study relies on existing clinical data collected for the purposes of care delivery, including records of genetic test ordering, completion, and results obtained for the purposes of clinical care and quality improvement from the EHR and genetic testing companies. These data will be aggregated into implementation metrics.
- **Confidentiality Protections**: Patient and provider data will be stored securely in a HIPAA-compliant manner, with strict access controls to prevent unauthorized use. Any data sharing across institutions will be done securely and in compliance with approved data transfer and usage agreements.

Given these safeguards, the risk posed to participants is comparable to that encountered in routine clinical care and quality improvement initiatives, fulfilling the minimal risk criterion.

## 8.3 Preservation of Patient and Provider Rights and Autonomy

The waiver of informed consent is structured to preserve the rights and autonomy of both patients and providers, ensuring ethical and equitable participation in the research.

***Respect for Patients**:*

- Patients may receive guideline-concordant germline testing, which is part of routine clinical care and consistent with national standards for hereditary cancer syndrome management.
- The project does not alter the standard of care but instead facilitates the delivery of care that is already recommended by clinical guidelines. Some patients should benefit directly from improved workflows.
- Patients will retain full autonomy over their medical decisions, including whether to accept or decline germline testing.

***Respect for Providers**:*

- Providers will receive the implementation strategies we will deploy, with full transparency about the deployment of clinical decision support (CDS) tools and workflows.
- Educational resources will empower providers to make informed decisions about germline testing orders without coercion or undue influence.
- Providers will retain autonomy in their clinical decision-making for each patient, with interventions designed to support—not replace—their judgment.

Both groups are protected from undue influence, and their rights and autonomy are preserved through careful design of the planned implementation strategies.

## 8.4 Impracticability of Conducting the Research Without Waiver

Obtaining informed consent from all patients and providers involved in the research would be impracticable due to the following factors:

***Nature of the Research**:*

- The implementation strategies (e.g., clinician education, clinician audit-feedback, CDS tools, workflow optimization) are embedded in clinical practice and indistinguishable from routine care. Requiring consent for these activities would create artificial barriers and could inadvertently bias outcomes by altering both clinician and patient behavior and participation.
- This project focuses on provider-level implementation strategies to increase guideline-concordant genetic test ordering by oncology care teams rather than clinical interventions, further reducing the appropriateness of obtaining individual consent.
- The goals of the research are to determine how the implementation strategies influence provider behavior when widely implemented. By consenting the providers, a bias would be introduced into the research, selecting for providers more willing to participate potentially biasing the outcomes. In addition, describing the rationale and goals for germline testing to the providers prior to the implementation of the study interventions, might alter their behavior outside of the study interventions, again potentially biasing the results.

***Burden to Participants and Providers**:*

- Requiring informed consent could impose unnecessary burdens on providers, diverting attention from patient care.
- Patients undergoing routine care may perceive the consent process as confusing or redundant, given that the research interventions align with routine medical practice.
- Any consent document would be the only record linking the provider or patient with the research data and obtaining and documenting consent would increase the risk of loss of confidentiality during any potential data breach.

Without waiver, the research would face insurmountable logistical and operational barriers making it impracticable to conduct the study at scale.

# 9. Implementation Outcome Measures

Using the REAIM QuEST framework, each of the outcomes below will be assessed separately for each eligible cancer type.

### 9.1 Primary implementation outcome

*Reach - genetic testing order:*
Number of eligible cancer patients with a germline genetic test ordered by an oncology care team provider, or associated with an oncology visit, within 7 days of an oncology encounter divided by the number of eligible cancer patients seen by the oncology care team (primary).

Qualitative data collected from the oncology care team will focus on the factors that contributed to their ability to identify patients for germline genetic testing and get the testing ordered and completed.

### 9.2 Secondary implementation outcomes

*Reach – completed genetic test:*
Number of eligible cancer patients completing germline testing order (e.g., have a test resulted, including sample failures) that was placed by their oncology care team divided by the number of eligible cancer patients with an order placed by that oncology care team (secondary).

Note, in secondary analyses of both ways we define reach, we will investigate whether reach is equivalent based on representativeness across different patient characteristics (e.g. age, cancer type, cancer stage, patient demographics).

*Effectiveness:*
Change in the number (or percentage) of patients with a molecular diagnosis of a hereditary cancer predisposition syndrome (e.g., a pathogenic/likely pathogenic germline genetic test result). These results are a proximal indicator of improving health outcomes for those with pathogenic germline variants.

Qualitative interviews of oncology team members will collect perceived effectiveness of testing all guideline-eligible cancer patients, perceived impact of having the test result on patient care, and reasons for differences in test ordering[21].

*Adoption:*
Adoption of mainstreaming by oncology care teams (percentage or number of oncology care teams ordering germline testing on at least one eligible patient divided by the number of eligible oncology care teams). We will assess the change in adoption at the provider and facility level over time. We will also assess the number of referrals to genetics-trained professionals prior to testing to distinguish mainstreaming from standard workflows.

Qualitative data collection with the oncology care team will focus on understanding their interest and decision to adopt the ordering of germline testing with their eligible patients.

Factors that were not addressed by strategies but would be of interest to the team will be elicited.

*Implementation:*
Fidelity to implementation strategies:
We will track implementation strategies using tools such as the Longitudinal Implementation Strategy Tracking System (LISTS)[22]. We will measure fidelity to the core components of the implementation strategies listed below.

- Provider education: Sites will report the number of oncology care teams who were trained and the number of clinician education sessions.
- Patient education: As available, sites will report on the number of patients who received educational materials or information resources through mechanisms amenable to automated tracking (e.g., distribution through the patient portal). Qualitative assessments based on how often a provider used patient education materials will also be gathered as available.
- Facilitation: We will use established facilitation tracking logs for site facilitators to document their activities.
- Audit and feedback: We will ask sites to provide the number of audit and feedback reports delivered to the oncology care teams.
- Peer support: Sites will report the number of peer support, or facilitations, that occurred by site champions to other team members.
- EHR strategies: Sites will provide details related to their existing EHR strategies; as well as provide documentation about changes to optimize their EHR strategies over the course of the project.

Adaptations to implementation strategies:
To monitor adaptations to implementation strategies, we will use FRAME-IS (Framework for Reporting Adaptations and Modifications to Evidence-based Implementation Strategies), a structured tool designed to systematically document changes made to implementation strategies in healthcare and other applied settings[23]. Sites will report on adaptations to each strategy listed above as implemented at their site. Adaptations will be assessed at least once during each phase of implementation.

Interviews with the oncology care team will assess the fidelity of strategy implementation, adaptations that were made (if any), the intensity of strategy implementation (and changes in dosage during the study), and how the teams' preferences and choices were integrated into implementation fidelity and adaptation throughout the study. For patient-education materials, interviews with providers will assess the fidelity of strategy delivery.

Qualitative data collection will also elicit how each of the selected strategies 1) improved their ability order testing, 2) facilitated patient buy-in, tracking and results monitoring, and communicating results to patients, and 3) improved patient treatment options. We will focus on identifying remaining barriers to care delivery and elicit suggestions for improvement.

Timeliness:
To monitor the impact of the mainstreaming intervention on timeliness of germline genetic testing, we will assess the time from the relevant oncology visit to genetic test order excluding patients already tested prior to implementation phase. As available at each site, we will also assess time from diagnosis to the genetic test order, and time from genetic test order to collection, processing, and accessioning of a specimen as well as time from specimen accessioning to report.

*Maintenance:*
To assess maintenance of the mainstreaming of germline genetic testing, we will assess primary reach (genetic testing order) and secondary reach (completed genetic testing) approximately 12-24 months after the end of active implementation strategies.

## 10. Data Collection

Data will be collected from the following sources as available at each site:

**Electronic health records (EHR):** Each site will collect structured data from its EHR and associated data warehouses, including demographics, ICD codes, problem list entries, and other study determinants and outcomes. Chart reviews may be used if needed to supplement these data. Clinical records outside the EHR may be used if consistent with local practices (*e.g.*, genetic testing tracking sheets in spreadsheets or in REDCap). Unstructured data may be processed, e.g., through natural language processing or large language model approaches approved by the local institution for the handling of such data, to extract relevant structured data from source unstructured data.

**Reference laboratory data:** As needed, sites will work with one or more clinical reference laboratories that perform genetic testing for their patient populations to obtain data related to the type of genetic tests ordered along with other relevant attributes of the tests such as results, completion status, ordering provider, and relevant dates such as order date, specimen collection data, specimen sending date, specimen receipt date, and report generation date.

**Qualitative data**: In line with our second aim, qualitative data most appropriate for the implementation issues to be understood will be collected via efficient and purposive methods. This may include, but is not limited to, individual interviews, group discussions, meeting minutes, and/or observations with key informants (e.g., implementation team members, oncology care teams, and administrators) and study evaluation staff throughout the cycles of implementation. Qualitative data collection will be completed by a study team member using a standardized set of questions and probes or other appropriate collection tools. Other qualitative data may include workflow observations, meeting minutes, and decision logs **(Table 4).**

**Table 4:** Example Qualitative Interview Questions

| RE-AIM Outcome | Potential Informants | Example Data to be Collected |
|---|---|---|

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|---|---|---|
| **Reach** – ability to identify patients | Implementation team | What factors contributed to your ability to identify patients for germline genetic testing?<br><br>What factors optimize a site's ability to increase patients' uptake of germline genetic testing when offered to them?<br><br>What barriers are driving quantitative differences in germline genetic testing at your site? |
| **Effectiveness** – What health value clinicians ascribe to mainstreamed germline genetic testing | Implementation team | Is ordering germline testing part of your current practice when caring for patients with (breast/colon/pancreatic) cancer?<br><br>To what degree do you think mainstreaming will assist you in identifying patients with hereditary risk? |
| **Adoption** – Why clinicians offer (or do not offer) germline genetic testing | Implementation team | What factors currently contribute (support or limit) to your decision to offer germline genetic testing?<br><br>What changes or interventions are needed to improve the implementation of germline genetic testing with oncology care teams?<br><br>Imagine that this mainstreaming project fails spectacularly. What do you think would be the cause(s)?<br><br>Thinking about the specific steps – patient identification, referral, and follow-up – what factors made it hard or easy to do each of those things?<br><br>Thinking back over the different strategies employed to mainstream germline genetic testing with oncology care teams, please talk about the impact of **educational initiatives** (PHASE 1). |

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| | | Thinking back over the different strategies employed to mainstream germline genetic testing with oncology care teams, please talk about the impact of **audit and feedback initiatives** (PHASE 2).<br><br>Thinking back over the different strategies employed to mainstream germline genetic testing with oncology care teams, please talk about the impact of **facility/clinical champions** (PHASE 1).<br><br>Thinking back over the different strategies employed to mainstream germline genetic testing with oncology care teams, please talk about the impact of **EMR changes** (PHASE 3). |
| **Implementation** – how and why adaptations are made to the implementation strategies (provider education, patient education, facilitation, audit and feedback, and EHR optimization) | Implementation team | Tell us about your experience implementing mainstreaming.<br><br>What is your understanding of the implementation approach used by your health system?<br><br>Did you make any changes to the implementation approach? Why and who decided?<br><br>Do you have any suggestions about additional ways to make mainstreaming work? |
| **Maintenance** – understanding program sustainability | Implementation team | Now that mainstreaming has been implemented for 18 months, what has made it hard or easy to maintain this approach?<br><br>What support, if any, would you need to continue the mainstreaming model?<br><br>Without additional support, how likely are you to continue to offer germline genetic testing to your |

| | | |
|---|---|---|
| | | patients? What factors influence your ability to continue offering this testing?<br><br>What existing infrastructure could support the ongoing use of the mainstreaming model? |

All data collection by the evaluation team will be conducted in a HIPAA-compliant manner.

**Data Sharing Procedures**
Each individual site may conduct data analyses for evaluation or intervention development and maintenance purposes. In addition, each site will provide a Limited Data Set to the Coordinating Center to enable centralized data analyses. Data will be shared in a secure, HIPAA-compliant manner with relevant data transfer and use agreements in place.

## 11. Risks and Benefits

The study may benefit healthcare providers by providing implementation strategies for delivering guideline-directed care and through streamlining and simplifying the process of ordering and delivering germline genetic testing to patients. As a result, guideline-concordant germline genetic testing for cancer patients may increase. Patients may receive more personalized care to help better inform cancer treatment and risk management.

This study poses minimal risks to providers. Providers' workflows and workloads may experience change as a result of the implementation strategies, but the implementation strategies that will be delivered to providers do not affect clinician health or safety. The implementation strategies delivered to providers are only intended to improve their care workflows and to promote the ordering of guideline concordant germline genetic testing and thus are expected to improve outcomes for their patients.

Patients are not exposed to implementation strategies in this study, but, rather, are cared for by oncologists exposed to these strategies. Risk to patients is minimal, as these strategies are all common methods used in quality improvement initiatives, and treating oncologists will still use clinical judgment in the care of these patients. All patient data are from clinical interventions performed as part of clinical care. This data will be obtained as described above.

One risk of this project for both patients and providers is loss of privacy as a result of research data collection procedures or data breach. To minimize these risks, a number of procedures will be put in place. Private health information is confidential and will be treated using HIPAA-compliant procedures, managed using HIPAA-compliant software (e.g., REDCap), and stored on HIPAA-compliant servers. Protected health information (PHI) will only be stored on HIPAA-compliant computing equipment that is cleared by institutional policies for the handling of PHI. Only IRB-approved personnel or IT

infrastructure personnel with a need for access (e.g., members of the enterprise data warehouse team) will have access to PHI.

## 12. Safety Monitoring and Adverse Events (AEs)

Investigators will provide ongoing monitoring of all participants in the study. The participants are defined as the providers (oncology care teams) in this study that receive the implementation strategies regarding germline testing. Should any adverse event to study providers or their patients that could reasonably be attributed to the study arise, it will be reported to the local Principal Investigator(s) and coordinating center through a secure method such as a REDCap form on the study database. Any serious adverse events that could reasonably be attributed to the study will be reported to the local IRB within 10 working days of the PI's notification of the event. Non-serious adverse events that could reasonably be attributed to the study and instances of noncompliance with the protocol will be reported at the time of continuing review. The PI(s) will ensure that all AEs that could reasonably be attributed to the study will be graded according to severity and reported accordingly. These events will also be reviewed with the Network Steering Committee to determine if adjustment of the protocol is needed. Any identifying information will be removed before sharing details with other network sites.

**Adverse Event**

An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's involvement in the research, that could reasonably be considered attributable to the research. As the participants are the providers receiving guidance on germline genetic testing, adverse events are expected to be rare.

**Monitoring for Adverse Events**

The time interval during which participants will be monitored for the occurrence of adverse events begins at Time 0 (implementation of the first strategy as described in **Figure 3** in section 4.3) and ends at the completion of the last implementation strategy. Adverse events occurring before Time 0 or after the implementation follow up period is completed will not be collected. The PI(s) at each site will have primary responsibility for overseeing the monitoring, assessment, and reporting of adverse events. If study personnel identify a potential adverse event reasonably attributable to the study, the PI(s) will be immediately notified. The PI(s) will assess the seriousness, unexpectedness, and relatedness of the potential adverse event. The PI(s) will determine whether the event qualifies for recording and reporting. AEs that are serious or unexpected and are definitely or reasonably related will be reported; all others will not.

**Unanticipated Problems involving Risks to Subjects or Others**

Investigators will also report Unanticipated Problems involving risks to Subjects or Others ("Unanticipated Problems"), associated with study procedures **within 10 days** of the site investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that is unexpected given (a) the research procedures that are described in the protocol-related documents, and (b) the

characteristics of the subject population being studied; AND is reasonably related to participation, and suggest the research places the subjects or others at a greater harm of risk (including physical, psychological, economic, or social harm) that was previously known or recognized.

If any study personnel at a site become aware of an event that may represent an Unanticipated problem reasonably related to study participation, they will immediately contact the lead investigator for the site. The lead investigator at the site will assess whether the event represents an Unanticipated Problem reasonably related to study participation and will alert the Coordinating Center as well as document in a REDCap form. The Coordinating Center will report the Unanticipated Problem to the IRB within 10 days of becoming aware of the Unanticipated Problem.

**Protocol Deviations and Violations**

Investigators will also monitor for Protocol Deviations and Protocol Violations. Protocol Deviations and Protocol Violations are defined as follows:

- Protocol Deviation: An incident involving noncompliance with the protocol that typically does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the resultant data. Deviations may result from the action of the participant, investigator, or staff.
- Protocol Violation: Accidental or unintentional changes to the IRB approved protocol procedures that affect the subject's rights, safety, welfare, and/or the integrity of the resultant data.

Principal investigators will alert the CC and document any protocol deviations and violations. Protocol violations will be reported to the IRB within 10 days of the CC becoming aware of the event.

## 13. Study Withdrawal/Discontinuation

A waiver of informed consent is being requested for both providers receiving the study implementations and patients who may receive germline testing, given the nature of this research. As neither providers nor patients will be consented, they will not withdraw. Providers and patients can elect not to offer or undergo germline testing without withdrawing from the study. For provider interviews, if a provider decides they do not wish to continue an interview or later decides they do not want their responses included they can contact study staff to have the data removed prior to de-identification and inclusion in the dataset.

## 14. Summary of Analysis Plan

**Description of patient population:** To evaluate the effect of the implementation strategies on ordering of genetic tests for appropriate patients, the study population will consist of adult patients with colorectal cancer diagnosed at age < 50 years[17], pancreatic cancer diagnosed at any age[19], or female breast cancer diagnosed at age <66 years[18]. Age at diagnosis will be the age at first use of a relevant diagnostic code in the medical record

or cancer registry. Patients newly diagnosed with these cancers during implementation and patients previously diagnosed prior to launch of implementation and have not been tested are eligible for inclusion in the analytic dataset if they have at least one oncology visit for the targeted cancer during the study.

Patients with colorectal cancer will be excluded from primary analyses if they are diagnosed at age 50 or older and females with breast cancer will be excluded from primary analyses if diagnosed at age 66 or older. We may track these older patients for other relevant implementation outcomes. Individuals under 18 years of age will also be excluded from analysis.

**Target visit types:** Visit types included in the primary analyses include outpatient visits with a physician, advanced practice registered nurse/nurse practitioner, or physician assistant/associate either in person or via telemedicine (phone or video).

**Outcomes:** The primary outcome for Aim 1 is whether a visit resulted in an appropriate test order being issued (order made y/n). Similarly, for Aim 2, the primary outcome is test completed (y/n). Prior work suggests that most orders will be placed within a few weeks if not days of a visit. We expect this to be within approximately 7 days. However, prior to any analyses of the outcomes, the timing between visits and orders will be analyzed and an upper limit for acceptable time between them set. Time from order to test completion may be more skewed and the upper limit for completed test will be set accordingly per the observed distribution. The purpose of the upper limit is to censor outliers that are not reflective of the system processes being studied.

**Germline genetic test orders status:** Status includes complete (report available), specimen submitted/accessioned, pending specimen collection, and cancelled orders placed in the EHR or genetic testing laboratory portals. Completed test orders will include those with a report available, even if the test failed, and a submitted/accessioned specimen. Incomplete orders will include those in pending status after reaching the upper limit for follow-up as described above.

**Providers linked to visits:** The oncologist associated with the visit will be classified as the provider for that visit. Providers will see multiple patients over multiple visits, but patients may also see more than one provider over the course of their visits. Thus, when treated as random effects, patient and provider will be crossed, not nested.

**Unit of analysis:** The effective unit of analysis is the patient visit where a patient who meets inclusion criteria**,** has an office or telemedicine visit with a oncology care team member for a target cancer, and who has not had a germline genetic testing sample collected (or has an active order in place). The dates of the visits determine the implementation strategy phase, not the date of the test order or the test completion date for visits with those outcomes.

**Interrupted time-series analysis (ITS):** For Aim 1, we will perform a mixed effects logistic regression of test ordered by implementation phase and patient-level covariates with random intercepts for patient and provider. The Aim 2 analysis will be similar, replacing test ordered with test completed. As sites may encounter challenges

implementing a strategy as intended, be delayed in implementing strategies, or already be implementing strategies at a site (with no change in approach) sensitivity analyses will also be applied to account for site specific differences.

**Qualitative Data Analysis**: Framework analysis will be used to identify responses or information relevant to our questions about the drivers, core facilitators, and barriers to reach, effectiveness, adoption, implementation fidelity, and sustainability. Data will be coded by at least two independent coders to ensure that Cohen's Kappa is >85%. Analysis of oncology care team member interviews: Code maps, informed by the Consolidated Framework for Implementation Research (CFIR 2.0), will be developed to categorize data as follows: (1) Reasons for adopting the testing protocol, including barriers and facilitators driving change, and how adoption has changed with the introduction of each new strategy, (2) Description of the process of implementation as well as adaptations to program implementation (and adaptations that are still needed to ensure successful implementation) and (3) the experience of testing sustainability, including the impact of discontinuing any or additional implementation strategies during the maintenance phase.

## 15. Privacy/Confidentiality Issues

All patients and providers will be assigned a unique study ID for use in the analytic study database. Study personnel will access patients' electronic health records at multiple time points throughout the study: Access will occur when collecting baseline demographics and comorbidities; and when collecting clinical outcomes, which may occur up to 5 years after completion of study interventions. At no time during this study, its analysis, or its publication will patient or provider identities be revealed publicly. The minimum necessary data containing provider identities will be collected to execute study protocols; data will be de-identified in the analytic database by the coordinating center after receipt of the Limited Data Sets from clinical sites.

## 16. Follow-up and Record Retention

Patients may be followed after enrollment for up to five years after completion of the study interventions. Data collected from the medical record or collected from providers will be entered into a secure database (e.g., REDCap). A de-identified version of the dataset will be stored on the secure cloud environment called AnVIL (Genomic Data Science Analysis, Visualization, and Informatics Lab-space) created and managed by the sponsor NHGRI. All data will be maintained in a REDCap database at the Coordinating Center up to five years after completion of the study.

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