Statistical Analysis Plan

Increasing Germline Genetic Testing for Patients with Cancer (gLHS)

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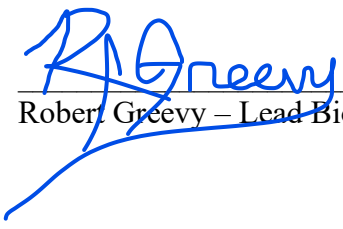

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Date

Introduction

Germline genetic 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 bundles of implementation strategies to increase germline genetic test ordering by oncology care teams for eligible breast, pancreatic, and colorectal cancer patients (i.e., mainstreaming). This document describes the analytic datasets and statistical tests to evaluate program implementation.

Study design

This study is an Interrupted Time Series, with no randomization used based upon the study design. The study is designed with one arm, with all participants receiving planned interventions. An alternative name for this study design is a quasi-experimental sequential cohort design (Happ et al., 2009). This description may more accurately reflect the primary analyses which will compare the phase 3 period to the baseline period. The primary analysis will focus on differences between pre- (baseline) versus post- (phase 3) interventions due to power considerations, but secondary and exploratory analyses will examine differences between each phase.

Randomization

No randomization is used in this study design.

Outcomes

Outcomes for this project were specified using the REAIM QuEST framework. This document describes the analytical plan for outcomes associated with Reach, Effectiveness, Adoption, and Maintenance, summarized in the table below.

RE-AIM Outcome	Definition
Reach Primary Outcome	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).
Reach Secondary Outcome	Number of eligible cancer patients completing germline genetic 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).
Effectiveness Secondary Outcome	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).
Adoption Secondary Outcome / Exploratory Outcomes	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). Increased adoption of mainstreaming by oncology care teams (percentage or number of oncology care teams with a relative increase in germline genetic test ordering rate of 10% or more between Phase 0 and Phase 3 divided by the number of eligible oncology care teams)

Maintenance Secondary Outcome	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.

Implementation Strategies

This study has a single arm of experimental participants. The experimental arm includes clinician members of oncology teams who care for adults with female breast, pancreatic, or colorectal cancer who will receive the implementation strategies described below.

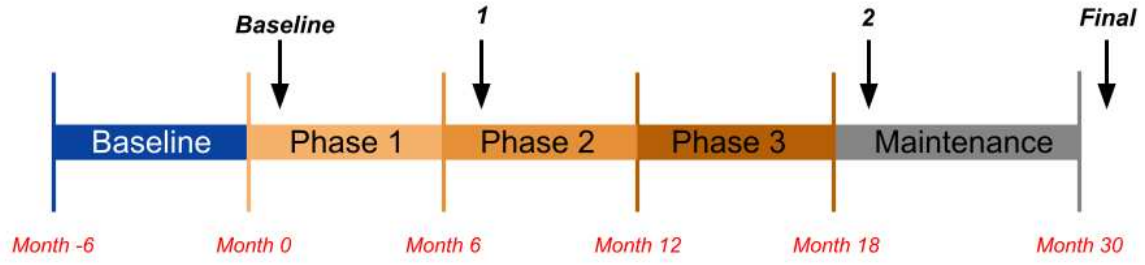
The study will deploy different strategy bundles across the clinical sites in three 6-month phases.
Phase 0 (Months -6 to 0): Baseline
Phase 1 (Months 0 to 6): Provider education/patient education
Phase 2 (Months 7 – 12): Facilitation with audit and feedback; champions; optimizing EHR
Phase 3 (Months 13-18): EHR build
Phase 4 (Months 19 to 30): Maintenance

Endpoints

Data freezes will occur after all sites have completed a given phase of the study. Each data freeze will include data from the beginning of the baseline phase to the specified cutoff date.

- The baseline data freeze will occur once all sites have initiated Phase 1.
- Data freeze 1 will occur after all sites have completed Phase 1.
- Data freeze 2 will occur after all sites have completed Phase 3.
- The final data freeze will occur after all sites have completed the study (ended Phase 4).

Freezing of datasets is to facilitate conducting research prior to the completion of the study, i.e. providing a fixed dataset that all teams can use. Whenever possible, analyses will be conducted using the latest dataset which will have undergone the most rounds of checking for completeness and accuracy.



Primary Endpoints:

The primary analysis will compare Phase 3 to Phase 0, i.e. the month 12-18 window vs month -6 to 0. Phase 3 strategies will rely on EHR builds which can be rolled out quickly without a long run-in period. Therefore, it is expected that the primary analysis will capture the effects of Phase 3 strategies. As strategies from Phases 1-3 may be discontinued in Phase 4 (maintenance), the maximum effect of the interventions is expected in Phase 3.

Secondary Endpoints:
Secondary analyses will compare across each phase of the study, with more details available in the "Secondary analysis" section. Secondary analysis examining maintenance outcomes will compare Phase 4 (maintenance) to Phase 3, i.e. the month 24-30 window vs. Month 12-18.

Study Population

Target Population:
The target population for this study includes clinician members of oncology teams who care for adults with female breast, colorectal, or pancreatic cancer. The clinical intervention is mainstreaming of germline genetic testing by oncology care teams for adult patients with colorectal cancer diagnosed under age 50, female breast cancer diagnosed under age 66, and pancreatic cancer diagnosed at any age. These cancer diagnoses and age ranges follow evidence-based guidelines describing indications for germline genetic testing for these patients (e.g., the National Comprehensive Cancer Network, American Society of Clinical Oncology-Society of Surgical Oncology).

Sample Size Considerations:
To inform the power analysis, we used the following assumptions:

1. The primary outcome as described in the "Outcomes" section will be assessed at Phase 0 and during Phase 3.
2. The main statistical comparison will be a test of whether the rate of germline genetic testing orders changes from Phase 0 to Phase 3.
3. Using pilot data from n = 4 of the included sites (VA, Geisinger, Indiana, and Utah), we obtained estimates of the following:
    a. The total number of oncology care team clinicians available to order tests for each type of cancer (female breast, colorectal, pancreatic)
    b. The total number of patients available for testing at baseline, including recently and not-recently diagnosed patients
        i. Patients newly diagnosed with these cancers during implementation are defined as recent cases and patients previously diagnosed prior to launch of implementation are defined as not recent cases.
    c. The total number of patients available for testing during follow-up, accounting for patients who receive a test order or who die between baseline and follow-up and the addition of new recently diagnosed patients over the course of the study phases
    d. The baseline testing rate prior to intervention; for VA, this accounted for different testing rates for the recently vs. not-recently diagnosed patients; for the other 3 sites (Geisinger, Indiana, Utah), the testing rate was assumed to be the same for recently and not-recently diagnosed patients
4. Based on data from the VA site, the 6-month mortality rate for patients is expected to be approximately 0.7% on average across cancer types.
5. The intracluster correlation coefficient for patients with the same clinician will be 0.15. The coefficient was selected as an estimate consistent with what has previously been observed for within-provider correlation in outcomes.

6. The minimum detectable effect would be expressed as an odds ratio or risk difference contrasting the % of patients receiving a germline genetic test order at months 12-18 during Phase 3 vs. Phase 0
7. For statistical tests of whether there was a change in the rate of testing from Phase 0 to Phase 3, we assumed an alpha of 0.05 and power >= 0.8.
8. We computed the minimum detectable effect size using a simple analytic formula that incorporates a design effect due to the intracluster correlation coefficient and via simulation.
9. The final estimates of the minimum detectable odds ratio or minimum detectable difference in the proportion of patients with a germline genetic test order were derived from site-specific estimates, using the most conservative set of assumptions (3a-d).

Comparing Phase 0 to Phase 3:

- The minimum detectable odds ratio (via simulation) would be 1.17 for Breast Cancer, 1.70 for Colorectal Cancer, and 1.31 for Pancreatic Cancer.
- The minimum detectable difference in the proportion tested (via simulation) would be an absolute difference of 3.7% for Breast Cancer, 8.1% for Colorectal Cancer, and 5.2% for Pancreatic Cancer.
- The minimum detectable difference in the proportion tested (using an analytic formula with a design effect) would be an absolute difference of 6.0% for Breast Cancer, 7.6% for Colorectal Cancer, and 6.8% for Pancreatic Cancer.

Analysis dataset

Description of patient population

Eligible patients have 1) had a diagnosis of a target cancer and 2) had an oncology visit during the project period.

Diagnosis
Eligible if the patient has ever had a diagnosis of colorectal cancer at ages less than 50 years old; OR female breast cancer diagnosed at ages less than 66 years old; OR pancreatic cancer diagnosed at any age. *Note*: Cancer diagnoses and associated age at diagnosis can come from either cancer registry data or EHR data. If both cancer registry data and EHR data are available for a particular cancer type, use age at first diagnosis for that cancer type-based cancer registry data. ICD-O/ICD-10 and ICD-9 codes are used to identify colorectal, breast, or pancreatic cancer cases in each health system.
Patients newly diagnosed with these cancers during implementation (recent cases) and patients previously diagnosed prior to launch of implementation (not recent cases) and have not been tested are eligible for inclusion in the analytic dataset.

Visit
A visit is defined as a patient having a medical oncology or surgical oncology visit at one of the included gLHS health systems or clinics (as defined by each participating health system), during the Phase 0 - 4 period. *Note*: All completed, scheduled outpatient visit types should be included, including scheduled ambulatory or scheduled telehealth visits; no shows or cancelled

appointments should not be included. Eligible visits must have a theoretical probability of having a test ordered greater than zero.

Description of provider population
Clinician members of the oncology team who have a visit with an eligible cancer patient, as defined above, during Phase 0 to 4 of the study period. Oncology care team members may include but are not limited to advanced practice providers, nurse navigators, case managers, medical oncologists, and/or surgeons.

Description of germline genetic test order
This study will examine germline genetic testing and associated orders for hereditary cancer syndromes. Status includes complete (report available), specimen submitted/accessioned, pending specimen collection, and cancelled orders placed in the EHR or genetic testing laboratory portals. Test ordered is defined as any test with a date of test ordered. Only test ordered is examined in the primary outcome, with analyses of test completion performed as a secondary analysis. Test completed is defined as any test which has a date of specimen collection, receipt by lab, or results reported. Due to inclusion of tests collected and received by the lab, test completed may include tests that failed due to sample failures. Incomplete orders will include those in pending status after reaching the upper limit for follow-up as described in the Statistical Approach section.

Order will be attributed to clinician if ordering clinician can be identified. If not, the test will be attributed to an oncology care team clinician if placed within 7 days after an oncology encounter. If the order cannot be attributed to a clinician or is not placed within 7 days of a visit, the test will not be counted as a mainstream order attributed to an oncology clinician, but more broadly counted as a test ordered by any means examined in the secondary analysis. Patient will not be eligible in any subsequent visits due to no longer meeting eligibility criteria (having previous order). For example, this would apply to an order placed 8 days after an oncology visit – the order would be counted as a test order by any means but not a mainstream order.

Unit of observation
In lay terms, the unit of observation is each visit of a patient who, at the time of the visit, qualified for an order and had not had a germline genetic test order placed yet. The most granular unit of observation is the patient visit but may be aggregated to the provider and clinic level for interpretation based on the outcome of interest.

In technical terms, the effective unit of observation is the patient visit where a patient who meets inclusion criteria**,** has an office or telemedicine visit with an 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.

Statistical Approach

Our initial analysis will be descriptive in nature, summarizing information that characterizes the cohort and outcomes. Then, we will proceed with inferential analysis to answer the main study question. Then, we will compare the secondary endpoints between study groups.

Descriptive Analysis
To characterize the study sample, baseline demographic and clinical data will be described overall and by group. Categorical variables will be described using frequencies and proportions, and continuous variables will be described using means and standard deviations, as well as medians and interquartile ranges. Missingness will be reported for each variable. Box plots, violin plots, and/or histograms may be used to describe the data graphically.

At a minimum, the following variables will be described at time of enrollment:

- Age at first oncology visit during study period (years)
- Sex (male, female, unknown)
- Race (American Indian / Alaska Native, Asian, Black, Native Hawaiian / Pacific Islander, White, Multiple / Not Otherwise Specified, Another Race)
- Ethnicity (Hispanic, Non-Hispanic, Unknown)
- Census tract area deprivation index
- Cancer stage *
    - Cancer stage will be collected but may be difficult to extract and link to specific oncology visits.
- Cancer Type (breast, colorectal, pancreatic)
- Additional covariates which may be predictive of testing rates may be collected (e.g. initiation of hospice)

We will describe all the outcome variables overall and grouped by study arm using the same approach as for the demographic data. Summary statistics and graphical representations may be displayed, and missingness will be reported for each variable.

Sensitivity analyses will be performed to assess the impact of missing data on results. If the levels of missing data are within typical ranges, data will be imputed using multiple imputation via chained equations (MICE) with results combined following Rubin's rules. If missingness of a variable is substantial it will be excluded from analyses.

No statistical comparisons between groups will be done for this descriptive analysis.

Definitions for "Outcome Window"
The subjects will be analyzed during "outcome windows" of time for which they may have a genetic test ordered.

Primary Analysis Outcome Window
Because the likelihood of testing is anticipated to drop-off dramatically within the first six months after first eligible visit (defined under "Visit" in the Analysis Dataset section), the primary analysis will focus on the six-month window after first eligible visit. The recorded outcome window will start at date of first eligible visit and extend to the earliest date of the

following: test-ordered, censored due to death (DOD), left-system/lost-to-follow-up (latest EHR medical encounter date + 180 days), or administratively censored (6 months post visit date). Operationally, test ordered and administrative censoring will be the main determinants of the outcome window.

Only visits that occur during the Phase will contribute to the specific phase. For example, if a patient has a visit 3 months into Phase 1, 3 months of follow up will occur during Phase 1 and 3 months will occur during Phase 2.

Note: the 6-month window was chosen as the period of time in which almost all tractable cases should receive testing under a successful intervention. The appropriateness of the 6-month window as well as timeframes for censoring of patients will be verified using baseline and phase one data and adjusted as needed prior to any analysis of phase 3 data.

Secondary Analysis Outcome Window
Because the interventions may impact testing rates for recently and not recently diagnosed cases differently, secondary analyses will separately analyze visits based upon a six-month window from initial diagnosis date rather than date of first eligible visit. Both recent cases where the eligible visit occurred during the six-month window after diagnosis and visits that occur outside the six-month window from initial diagnosis date will be analyzed.

Recency of diagnosis may matter as some not recent cases will be tractable, i.e. testing could still occur for these patients, and some intractable, i.e. test will never occur for these patients due to patient choice, expected lifespan, etc. If most of the tractable cases received testing in Phases 1 and 2, this would leave only the intractable cases in Phase 3, making the testing rate in Phase 3 look lower by comparison. Moreover, if the intervention works, only intractable cases will make it past the 6-month outcome window. Successful intervention could show the testing rates for not recent cases spike at some point in the study, but then come back down as all the tractable cases get tested.

Primary Analysis
For the primary analysis, we will perform a mixed effects logistic regression of whether a genetic test was ordered by implementation phase and patient-level covariates with random intercepts for patient and clinician. Healthcare visits where a test should have been ordered will be included if they occurred during Phase 0 or Phase 3 and are considered recent cases.

The interpretation of the main analysis will be the relative increase in the odds of having a test ordered for visits in Phase 3 vs Phase 0. Statistical inferences will be based on the confidence intervals and p-values derived from the model. For descriptive purposes, the model's odds ratio will be translated to an absolute risk difference for the increased probability in genetic testing in Phase 3 relative to the rate of genetic testing in Phase 0.

Secondary Analyses

Secondary analysis will assess outcomes of reach (test completed), effectiveness, adoption, and maintenance. All outcomes besides maintenance will be assessed as a comparison between Phase 3 and Phase 0 as described in "Primary Endpoints" under the Study Design section.

For reach (tests completed), we will perform similar methods to the primary but swap the outcome (genetic tests ordered) for test completed and swap implementation phase for time. Effectiveness will be determined as the change in the percentage of patients with a completed test with a pathogenic/likely pathogenic germline genetic test result. Adoption will be calculated as the change in the number of oncology care teams ordering germline genetic testing on at least one eligible patient divided by the number of eligible oncology care teams. To assess maintenance, primary reach (genetic testing order) and secondary reach (completed genetic testing) will be calculated to compare Phase 4 (maintenance) with Phase 3, as described in the "Secondary Endpoints" under the Study Design section.

The data set will include healthcare visits where a test should have been ordered for the not recent cases only. Time will be calculated continuously as days from intervention start (start of Phase 1) to the earliest date of the following: test completed, censored due to death (DOD), left-system/lost-to-follow-up (latest EHR medical encounter date + 180 days), or administratively censored (end of study period). Time will be fit with a restricted cubic spline to allow for non-linear effects. The change in odds of genetic testing will be displayed graphically, showing the possible non-linear changes throughout the study period. This may be supplemented with pairwise comparisons of specific phases, e.g. Phase 2 vs Phase 1, or specified time-windows, as needed.

Exploratory and Sensitivity Analysis

Model checking: Robustness of the conclusions to modeling assumptions for the primary analysis will be examined by calculating 95% confidence intervals and p-values for the effect via bootstrapping at the patient level. If needed to achieve acceptable model performance, we will explore changing the distribution of random effects, link function, and/or overall model. If necessary, the bootstrap confidence intervals and p-values will be used for the primary and secondary analyses. Note that with the anticipated sample sizes, generating bootstrap confidence intervals for all analyses will be cumbersome, so reliable model-based estimates will be preferrable.

a) Exploratory analyses will stratify by clinical site, where the primary and secondary analyses will be run for each clinical site. Additional exploratory analyses stratifying by other factors such as those described under "Descriptive Analysis" under the Statistical Approach section are planned.
b) Analyses estimating the impacts on specific providers will subset to providers who were seeing patients throughout the baseline and phase 3 periods.
c) Exploratory analyses will examine increased adoption of mainstreaming by oncology care teams (percentage or number of oncology care teams with a relative increase in germline genetic testing ordering rate of 10% or more between Phase 0 and Phase 3 divided by the number of eligible oncology care teams). These exploratory analyses of adoption will supplement the planned secondary outcomes examining adoption.

d) Exploratory analyses of the impact of specific interventions will overlay intervention times with the continuous time effect (see secondary analyses above). This analysis will also be conducted after stratifying by site to explore site-specific interventions and seminal events (see b above).
e) Robustness to choice of censoring criteria will be explored. The primary analysis will be run under various censoring assumptions, including varying the window that defines a recent case.
f) Exploratory analyses of test ordered by any means, mainstream and non-mainstream tests.

Summary

This project seeks to close the identified care gap in genetic testing of hereditary cancer predisposition by evaluating a suite of implementation strategies expected to increase guideline-concordant germline genetic testing by oncology care teams (i.e., 'mainstreaming'). Identification of hereditary risk is critical for individuals with a cancer diagnosis, as it can have implications for treatment, surveillance, and testing of family members.

Appendix 1: Variable names from Data Dictionary

Variable	DD Form	DD Variable name	Purpose
Record ID	Multiple	record_id	Patient ID
Site ID	Multiple	site_id	Analyses
Age	Patient	year_of_birth	Demographics
Breast cancer diagnosis age	Patient	breast_cancer_dx_age3	Inclusion, Secondary analyses
Data source for breast cancer diagnosis date	Patient	breast_cancer_dx_date_source	Inclusion
Colorectal cancer diagnosis age	Patient	colorectal_cancer_dx_age3	Inclusion, Secondary analyses
Data source for colorectal cancer diagnosis date	Patient	colorectal_cancer_dx_date_source	Inclusion
Pancreatic cancer diagnosis age	Patient	pancreatic_cancer_dx_age3	Inclusion, Secondary analyses
Data source for pancreatic cancer diagnosis date	Patient	pancreatic_cancer_dx_date_source	Inclusion
Oncology visit	Oncology_Visit	onc_visit_age3	Inclusion

Gender	Patient	Sex	Demographics, Analyses
Race: American Indian/Alaska Native	Patient	race_am_indian_ak_native	Demographics, Analyses
Race: Asian	Patient	race_asian	Demographics, Analyses
Race: Black	Patient	race_black	Demographics, Analyses
Race: Native Hawaiian/Pacific Islander	Patient	race_native_hi_pi	Demographics, Analyses
Race: White	Patient	race_white	Demographics, Analyses
Race: Multiple/Not Otherwise Specified	Patient	race_multiple_nos	Demographics, Analyses
Race: Another Race	Patient	race_another	Demographics, Analyses
Ethnicity	Patient	ethnicity	Demographics, Analyses
ADI National Percentile	address_history	adi_national_percentile	Demographics, Analyses
RUCA Primary Code	address_history	ruca_primary_code	Demographics, Analyses
Smoking status	Patient	Smoking_status_current	Demographics, Analyses
Comorbidity score	Patient	comorbidity_score	Demographics, Analyses
Stage of cancer at Dx using AJCC staging	Patient	breast_cancer_stage_dx	Demographics, Analyses
Stage of cancer at Dx using AJCC staging	Patient	colorectal_cancer_stage_dx	Demographics, Analyses
Stage of cancer at Dx using AJCC staging	Patient	pancreatic_cancer_stage_dx	Demographics, Analyses
Age at Oncology Visit Date	oncology_visit	onc_visit_age3	Primary analyses. inclusion
Provider ID	oncology_visit	onc_provider_id	Primary analyses

Was this visit a telehealth visit?	oncology_visit	onc_visit_telehealth	Primary analyses
Provider specialty	Provider	provider_speciality	Primary analyses
Age at Other Visit Date	other_visit	other_visit_age3	Primary analyses
Provider ID	other_visit	other_provider_id	Primary analyses
Age at most recent visit	other_visit	recent_visit_date_age3	Censoring
Was this visit a telehealth visit?	other_visit	onc_visit_telehealth	Primary analyses
Was this visit a telehealth visit?	genetics_visit	genetics_visit_telehealth	Primary analyses
Age at test order	germline_test_order	test_order_age3	Primary analyses, inclusion
Was the genetic test completed?	germline_test_order	germline_is_done	Secondary analyses
Age specimen collected	germline_test_order	specimen_collected_age3	Secondary analyses
Age specimen received by lab	germline_test_order	specimen_receipt_age3	Secondary analyses
Age specimen reported	germline_test_order	specimen_reported_age3	Secondary analyses
Order delivery model	germline_test_order	order_delivery_model	Exploratory analyses
Ordering user ID	germline_test_order	ordering_user_id	Inclusion
Was germline test confirmed as hereditary cancer syndrome test?	germline_test_order	her_cancer_test	Inclusion
Order delivery model	germline_test_order	order_delivery_model	Inclusion
Implementation age Phase 0	Patient	implementation_phase_0_age3	Primary analyses
Age at Phase 1 start	Patient	implementation_phase_1_age3	Primary analyses
Age at Phase 2 start	Patient	implementation_phase_2_age3	Primary analyses

Age at Phase 3 start	Patient	implementation_phase_3_age3	Primary analyses