Supplemental information

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Glossary of terms: The following glossary represents a compilation of definitions based in part on published information from the Centers for Disease Control and Prevention, ClinGen, PGS catalog, and the National Cancer Institute.

Analytic validity: A test's ability to measure the genotype of interest accurately and reliably.

Ancestry: Patterns of genetic variation corresponding to where an individual's ancestors lived.

Ancestry-adjusted PRS: A PRS that has had the z-score calibrated based on the genetic ancestry observed in the participant data using calibration model parameters derived from a large set of diverse individuals.

Clinical actionability: A known ability to intervene and thereby avert a poor outcome due to a previously unsuspected high risk of disease.

Clinical utility: The likelihood that a test will, by prompting an intervention, result in an improved health outcome.

Clinical validity: The predictive value of a test for a given clinical outcome.

Cross-ancestry PRS: A PRS that has been derived and validated using genome wide association study (GWAS) data from two or more ancestral populations.

Family history risk: Inherited disease risk associated with the presence of disease in one or more 1st or 2nd-degree family members.

Monogenic risk: Disease risk associated with a pathogenic or likely pathogenic variant in a single gene.

Polygenic risk score (PRS): A polygenic score (PGS) aggregates the effects of many genetic variants into a single number which predicts genetic predisposition for a phenotype.

Supplemental Table S1: eMERGE workgroup and goals.

Workgroup	Goal
Comprehensive Risk Assessment & Return	Oversees the content and design of the GIRA, including harmonizing return materials and care recommendations. Coordinates return methods across the sites.
EHR Workflow & Infrastructure	Develops the R^4 data flow across the network, establishes data dictionaries for structured data used for reports, and coordinates strategies for how sites will integrate the GIRA within their EHRs.
Phenotyping	Develops the clinical data flow from site EHRs to the centralized R^4. Establishes metrics and data dictionaries for data variables. Integrates data into AnVIL and performs phenotypic data refreshes.
PRS Validation & Evaluation	Assessed and selected the PRS's to be used in the study, workflow and data, and performed cross-ancestry validation of the selected eMERGE conditions. Works on PRS retrospective validation and AnVIL genomic tools.
Provider Uptake & Outcomes	Establishes baseline outcomes, uptake measurements, and control group for analysis, and examines the impact of the study with an ELSI lens through participant and provider surveys and interviews.
Recruitment, Retention, sIRB & ELSI	Focused on recruitment and retention strategies aimed at both individuals and providers. Harmonized educational material for individuals and providers, training for study staff and website. Manages and submits IRB protocol and amendments. The ELSI members implemented site specific ELSI projects in year 1 and provide overall network guidance.

Supplemental Table S2: Repository links to polygenic risk score pipeline methods.

Pipeline	Resource	Link
PRS	GitHub	https://github.com/broadinstitute/palantir-workflows/blob/v0.10/ImputationPipeline/PRSWrapper.wdl
PRS	Dockstore	https://dockstore.org/workflows/github.com/broadinstitute/palantir-workflows/PRSWrapper:v0.10?tab=files
Imputation	GitHub	https://github.com/broadinstitute/warp/blob/Imputation_v1.1.1/pipelines/broad/arrays/imputation/Imputation.wdl
Imputation	Dockstore	https://dockstore.org/workflows/github.com/broadinstitute/warp/Imputation:Imputation_v1.1.1?tab=info

Supplemental Table S3. GIRA polygenic risk score (PRS) result text and odds ratios.

Condition	PRS result text in GIRA
Asthma	A high polygenic risk score for asthma was found in this individual. A high polygenic risk score is associated with up to 2 times increased risk for developing asthma relative to a person not in the high risk category. The data is based on pediatric European, African, and Hispanic populations. Information is insufficient or not available for populations of other descent.
Atrial fibrillation	A high polygenic risk score for atrial fibrillation was found in this individual. A high polygenic risk score is associated with approximately 2 times increased risk for developing atrial fibrillation relative to a person not in the high risk category. The data is based on populations of African, European, and Hispanic/Latino descent. Information is insufficient or not available for populations of other descent.
Breast cancer	N/A for PRS text. Integrated score text: Based upon the participant's genetic risk, family history, and personal factors including age, sex, body mass index, breast density, reproductive history, and hormonal exposure, the lifetime risk of breast cancer to the age of 80 is <xx>. The average woman has a lifetime risk of breast cancer of 12%, so this risk is higher.
Chronic kidney disease	A high polygenic risk score for chronic kidney disease was found in this individual. A high polygenic risk score is associated with 2 to 4 times increased risk for developing chronic kidney disease relative to a person not in the high risk category. The data is based on populations of European, Asian, Hispanic/Latino, and African descent. Information is insufficient or not available for populations of other descent.
Colorectal cancer	N/A no PRS generated
Coronary heart disease	A high polygenic risk score for CHD was found in this individual. A high polygenic risk score is associated with 1.7 to 2.3 times increased risk for developing CHD relative to a person not in the high risk category. The data is based on populations of European, Hispanic/Latino, East Asian, South Asian, and African descent. Information is insufficient or not available for populations of other descent.

Hypercholesterolemia	A high polygenic risk score for hypercholesterolemia was found in this individual. A high polygenic risk score is associated with 3 to 4 times increased risk for developing hypercholesterolemia relative to a person not in the high risk category. The data is based on populations of African, European, Hispanic/Latino and Asian descent. Information is insufficient or not available for populations of other descent.
Obesity	A high polygenic risk score for obesity was found in this individual. A high polygenic risk score is associated with 2 to 6 times increased risk for developing obesity relative to a person not in the high risk category. The data is based on populations of African, European, Asian, and Hispanic/Latino descent. Information is insufficient or not available for populations of other descent.
Prostate cancer	A high polygenic risk score for prostate cancer was found in this individual. A high polygenic risk score is associated with 3 to 3.5 times increased risk for developing prostate cancer relative to men not in the high risk category. For the purpose of shared decision-making, high polygenic risk score is equivalent to a positive family history for prostate cancer. The data is based on populations of African, European, Asian, and Hispanic/Latino descent and validated in populations of African and European descent. Validation information is insufficient or not available for populations of other descent.
Type 1 diabetes	A high polygenic risk score for type 1 diabetes was found in this individual. A high polygenic risk score is associated with 12 to 20 times increased risk for developing type 1 diabetes relative to a person not in the high risk category. The data is based on populations of African and European descent. Information is insufficient or not available for populations of other descent.
Type 2 diabetes	A high polygenic risk score for type 2 diabetes was found in this individual. A high polygenic risk score is associated with 3-7 times increased risk for developing type 2 diabetes relative to a person not in the high risk category. The data is based on populations of African, European, East Asian and Hispanic/Latino descent. Information is insufficient or not available for populations of other descent.

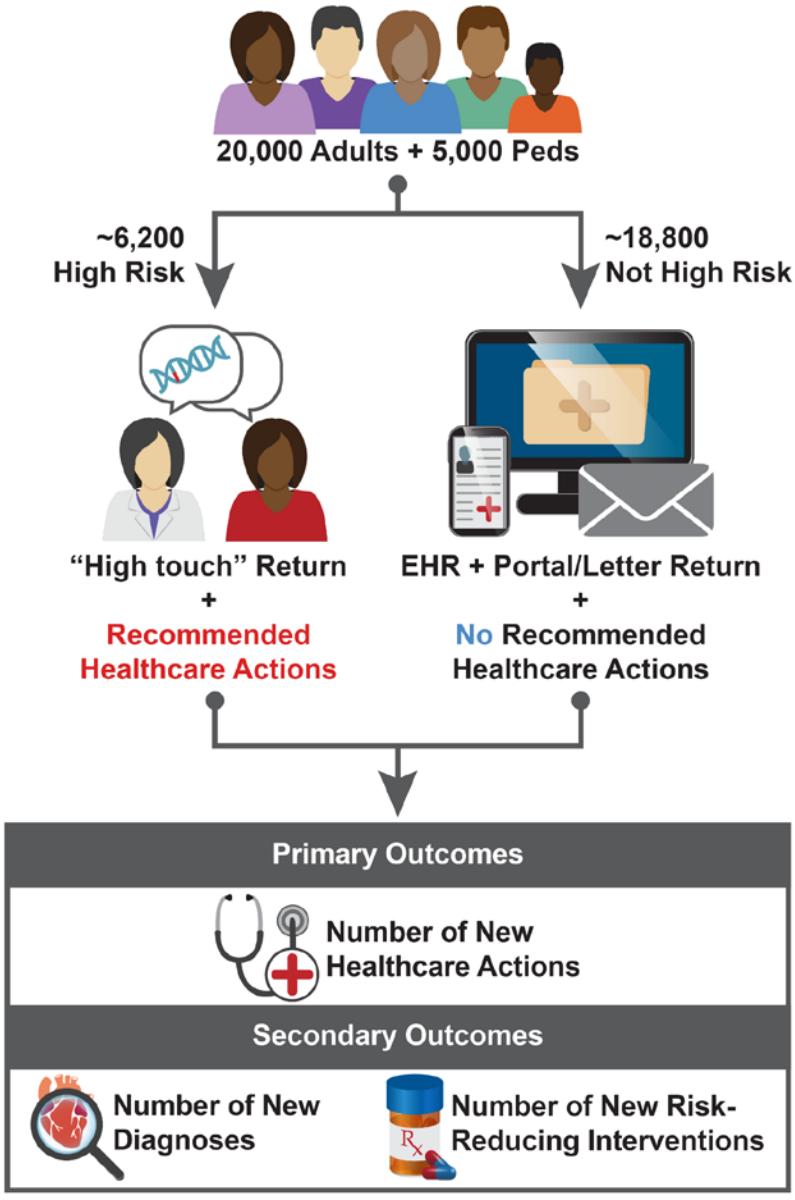
<u>Supplemental Table S4:</u> GIRA clinical recommendations for 'high risk' polygenic risk score return.

Condition	High risk PRS recommendation
Asthma[1,2] *(Pediatric only)*	● Arrange primary care provider office visit for asthma risk assessment and education. ○ History & physical exam for and education about signs & symptoms of airway obstruction. ○ Ask about wheezing / cough triggers in child's living environment(s) such as airway irritants (e.g. smoke), perennial allergens (e.g. mold, dust mites, pet dander), seasonal allergies and provide education for trigger mitigation. ● If history of wheezing / cough, ○ Assess need for a rescue inhaler/treatment at home. ○ Assess need for pre-medication (e.g. albuterol) prior to exercise. ○ Assess need for controller inhaler or daily treatment. ○ Consider referral to asthma specialist (e.g., pulmonologist, allergist). ● If asthma diagnosis suspected: ○ Install an asthma action plan. ○ Consider referral to asthma specialist (e.g., pulmonologist, allergist).
Atrial fibrillation[3–5] *(Adult only)*	● Assess for symptoms that suggest participant may have atrial fibrillation ● Assess for and manage other atrial fibrillation risk factors such as age >65, high blood pressure, diabetes, heart failure, prior stroke, renal insufficiency, hyperthyroidism, obesity, and sleep apnea, if present. ● Emphasize a healthy lifestyle: ○ Exercise regularly ○ Maintain healthy body weight ○ Heart-healthy diet ○ Smoking cessation if a smoker ○ Limit alcohol intake ● In those age ≥40 and based on symptoms or findings consider further cardiac screening that may include: 12 lead electrocardiogram (ECG), cardiac monitoring based on frequency of symptoms (2-14 day monitor (e.g. Holter or Ziopatch), or wearable device with atrial fibrillation monitoring capabilities (if available and affordable).
Breast cancer (for integrated BOADICEA score)[6–8] *(Female; adult only)*	● Emphasize a healthy lifestyle: ○ Exercise regularly. ○ Maintain healthy body weight. ○ Diet rich in fruit and vegetables. ○ Limit alcohol intake. ● Consider consultation with a breast specialist about medications to reduce the risk of breast cancer (tamoxifen or other anti-estrogen medications). ● Consider risks and benefits of hormone replacement therapy. ● Consider annual mammogram starting at age 40 or 10 years before the

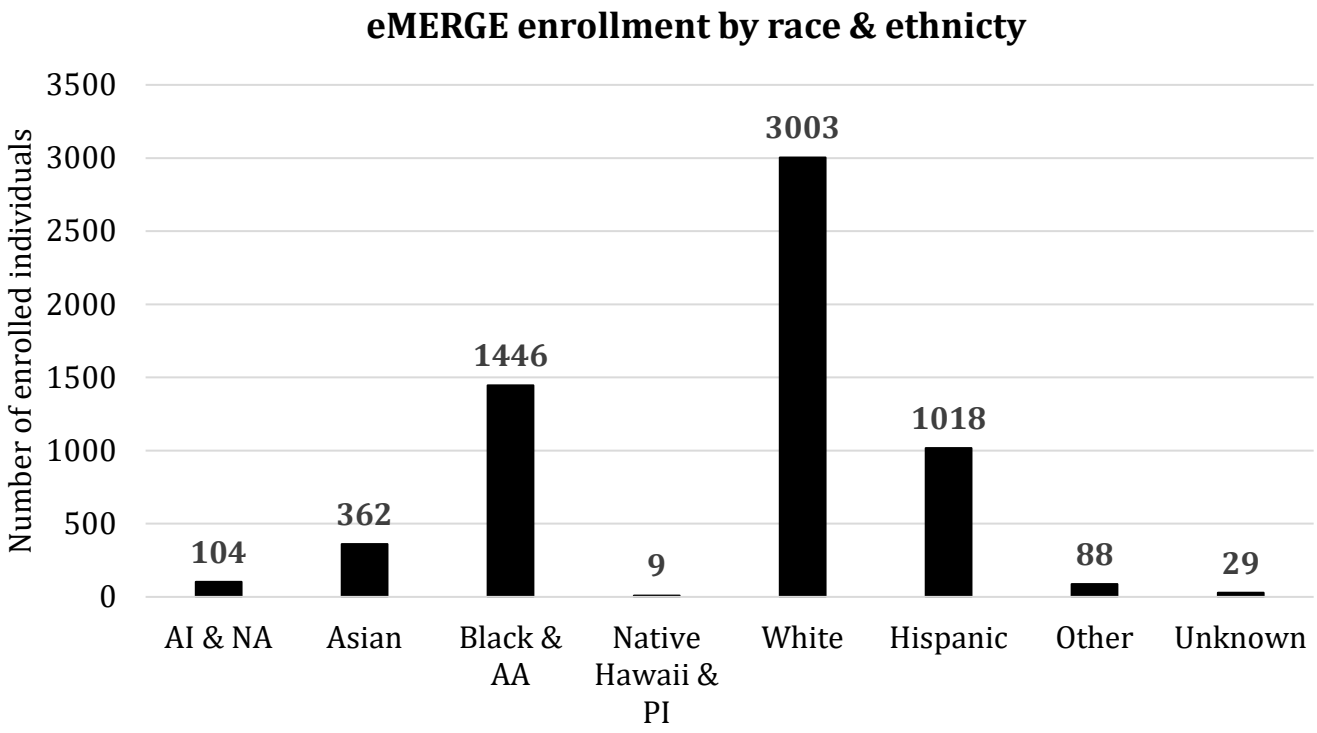
	youngest breast cancer in the family, whichever is younger. ● Consider annual breast MRI starting at age 40 or 10 years before the youngest breast cancer in the family, whichever is younger.
Chronic kidney disease[9–11] *(Adult only)*	● Check serum creatinine to assess renal function (eGFR). ● Check urine for protein by urinalysis, *If POSITIVE:* check urine albumin-to-creatinine ratio. ● Check blood pressure to assess for hypertension. ● Check hgbA1C and fasting blood glucose to assess for diabetes. ● Emphasize a healthy lifestyle: ○ Exercise regularly ○ Maintain healthy body weight ○ Maintain low salt diet (<2.3 g [0.08 oz] of sodium per day) ○ Limit alcohol intake ○ Smoking cessation if a smoker ○ Avoid NSAIDs and herbal or body-building supplements.
Coronary heart disease[12–14] *(Adult only)*	● Check a lipid profile and Lp(a). ● In those age ≥40, consider further screening such as with a coronary calcium scan and treatment with a statin to reduce CHD risk. Shared decision making is recommended. (In those age <40, carotid ultrasound to detect plaque/measure intima-media thickness, can be considered to assess for early disease, if such imaging modality is available). ● Treat risk factors such as high blood pressure, diabetes and high cholesterol, if present. ● Emphasize a healthy lifestyle: ○ Exercise regularly. ○ Maintain healthy body weight. ○ Heart-healthy diet. ○ Smoking cessation if a smoker.
Hypercholesterolemia[15] *(Adult only)*	● Check lipid levels. ● Consider initiation of lipid-lowering therapy (e.g., statin). ● Consider referral to a lipid specialist. ● Emphasize a healthy lifestyle: ○ Exercise regularly. ○ Maintain healthy body weight. ○ Heart-healthy diet. ○ Smoking cessation if a smoker.
Obesity[16–18] *(Pediatric & Adult)*	● Emphasize a healthy lifestyle by counseling this patient and their family regarding: ○ Healthy diet. ○ Exercise regularly. ○ Sleeping habits. ○ Screen habits. ● Assess for conditions related to obesity and recommend necessary

	treatment or ongoing screening as indicated. ● Consider referral to a dietician or nutritionist to assess current eating habits, identify opportunities for improvement and guide the patient in making healthy choices if indicated. ● Consider referral to a healthy weight program.
Prostate cancer[19,20] *(Male; adult only)*	● Consider beginning shared decision-making about prostate specific antigen (PSA) screening at age 40, and consider screening every year rather than every two years ○ Consider baseline digital rectal exam if PSA testing is done.
Type 1 diabetes[21–25] *(Pediatric only)*	● These results indicate that the patient is at increased risk for type 1 diabetes. ● Counsel patient and their family about the early symptoms of type 1 diabetes and when to alert their medical provider. ● Assess autoantibodies. ○ If negative consider repeating in a year depending on patient's age. ○ If positive for 2 or more antibodies counsel and consider referral to endocrinology or obtain a screening work-up with fasting glucose, urine glucose and hgbA1C. ● If symptoms of T1D are present, referral to endocrinology is recommended. ○ Additional testing by endocrinology or PCP at this stage may include but not necessarily be limited to the following: hgbA1C, regular fasting glucose screening, and at-home urinalysis for glucose and ketones ○ The frequency of these screening tests will be determined by endocrinology or PCP.
Type 2 diabetes[26] *(Pediatric & Adult)*	● Emphasize a healthy lifestyle: ○ Exercise regularly. ○ Maintain healthy body weight. ○ Eat a heart-healthy diet. ● For adults and children 12 and older: ○ Assess for symptoms such as polyuria and weight change. ○ Consider a biochemical screen with hemoglobin A1c or fasting glucose. ○ If elevated hgbA1c or fasting glucose: ▪ Consider prescription of metformin. ▪ Consider medical nutrition therapy consultation.

Supplement Figure S1: Expected study outcomes. The network expects ~6200 individuals to have at least one high risk condition on the GIRA. High risk GIRA will be returned via a 'high touch' method using in person or telehealth mechanisms and delivered by trained study staff, study MDs, or genetic counselors. The main outcome of interest is to determine if health care actions associated with care recommendations are more common among the high risk group.



<u>Supplemental Figure S2.</u> Race & ethnicity of individuals enrolled through December 2022. One major focus of the project is recruitment of underrepresented racial and ethnic groups, initial recruitment of 5671 individuals demonstrates approximately 47% non-white races and ethnicities. Individuals could indicate all races and if Hispanic ethnicity applied. 225 individuals indicated they were more than one race or ethnicity and 349 individuals indicated a race and Hispanic ethnicity during enrollment. AI & NA: American Indian & Native Alaskan; AA: African American; PI: Pacific Islander.



Supplemental Document 1. Example GIRA report. The GIRA report contains a summary page of high risk findings, in addition to more detailed information on the type of risk for a given condition, GIRA methods, as well as frequently asked questions. The example GIRA includes high risk findings for atrial fibrillation (pathogenic LMNA variant), breast cancer (BOADICEA score result > 25%), & T2D (PRS above threshold). When returned the report will also include the CLIA reports from Broad (PRS) and Invitae (monogenic), as well as the family health history pedigree from MeTree (Duke) as attachments (not shown here).

GIRA Report

Record ID	153

eMERGE Study Overview

eMERGE is a research network of 10 academic medical centers across the United States. It is funded by the national Human Genome Research Institute (NHGRI). The eMERGE study aims to find better ways to assess and manage patients' risk for future health conditions. eMERGE wants to learn if risk based on genetics, family health history, and personal health history, helps patients and their doctors make health care choices. This study is developing a Genome Informed Risk Assessment (GIRA) report. The GIRA report will have information about genetic risk, clinical risk, and family history for certain common conditions in adults and children.

Sections included in the GIRA Report

- Summary of findings
- Risk result breakdown
- Patient education page(s)
- Participant frequently asked questions
- Study methods and limitations
- BROAD Institute Polygenic Risk Report *(not included in supplement)*
- MeTree family health history pedigree *(not included in supplement)*
- Invitae eMERGE panel screen report *(not included in supplement)*

Site Contacts

Vanderbilt University Medical Center Principal Investigator XX X. XXXX, MD phone: XXX-XXX-XXXX email: XXX.XXXX@vumc.org	Vanderbilt University Medical Center Study Coordinator XXX XXXX, MPH, MBA phone: XXX-XXX-XXXX email: XXX.XXX@vumc.org

GIRA Report

Summary of Findings

emerge network ELECTRONIC MEDICAL RECORDS AND GENOMICS	**Name:**Jane Smith	**Provider:**_____
	DOB:1977-10-05	**Site ID:**Vanderbilt University Medical Center
	Sex at birth: Female	**Participant Lab ID:**Sample
	Date of Report:08/10/2022	

Genome Informed Risk Assessment (GIRA)

The following report is a summary of evaluated risk factors for common conditions. Common gene changes we tested for the conditions listed. Rare gene changes and family history were also included for some conditions. This study determined who is at high risk based on specific criteria for each condition.	Risks Evaluated:	
	Asthma*	Hypercholesterolemia
	Atrial fibrillation	Obesity/BMI**
	Breast cancer	Prostate cancer
	Chronic kidney disease	Type 1 diabetes*
	Colorectal cancer	Type 2 diabetes**
	Coronary heart disease	

* children only **adults and children

Summary of Findings

RESULT: This individual was found to be at high risk for one or more of the conditions evaluated. Being at high risk for a condition does not mean that this individual will definitely get that condition. When high risk for a condition is identified, recommendations are provided that may help reduce the risk of getting the condition or help treat the condition.**For participants already diagnosed with a condition, providers should continue with current treatment.**

This participant is at high risk for the following condition(s)

Gene: LMNA	Risk Category: **Monogenic Risk** **Associated Risks** • Increased risk for heart and neuromuscular conditions, including arrhythmia and cardiomyopathy. • See risk results page and attached Invitae report for additional information. **Care Recommendation:** • If your patient has not yet spoken to a genetic counselor regarding their results, we recommend referring your patient to a genetic counselor to discuss their results and potential next steps. • Recommend cardiac screening as below and/or cardiology consult. – Inquire for a personal history of palpitations or syncope – Assess pulse for irregularities. – 12 lead electrocardiogram (ECG). – Cardiac monitoring (consider 2-14 day monitor (e.g. Holter or Ziopatch), 30 day event monitor, or implantable loop recorder) with choice of monitoring based on history and physical findings. – Echocardiogram – Wearable device with heart monitoring capabilities (if available and affordable). • Please refer to the Invitae report and Invitae positive results guide for guidance. **References:** Nielsen JC, et. al.. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on risk assessment in cardiac arrhythmias: use the right tool for the right outcome, in the right population. J Arrhythm. 2020 PMID: 32782627Feinberg WM, et. al.. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med. 1995 PMID: 7864703Fox CS, et . al.. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. JAMA. 2004 PMID: 15199036.Yoneda ZT, et. al.. Early-Onset Atrial Fibrillation and the Prevalence of Rare Variants in Cardiomyopathy and Arrhythmia Genes. JAMA Cardiol. 2021 PMID: 34495297Perez MV, et. al.. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. N Engl J Med. 2019 PMID: 31722151

Breast Cancer:	Risk Category:**Integrated ScoreCare Recommendations** • Emphasize a healthy lifestyle: – Exercise regularly. – Maintain healthy body weight. – Diet rich in fruit and vegetables. – Limit alcohol intake. • Consider consultation with a breast specialist about medications to reduce the risk of breast cancer (tamoxifen or other anti-estrogen medications). • Consider risks and benefits of hormone replacement therapy. • Consider annual mammogram starting at age 40 or 10 years before the youngest breast cancer in the family, whichever is younger. • Consider annual breast MRI starting at age 40 or 10 years before the youngest breast cancer in the family, whichever is younger. **Professional Guidelines:** Breast cancer NCCN Guidelines **References:** Breast cancer screening and diagnosis version 3.2018, NCCN Clinical Practice Guidelines in Oncology. Therese B Bevers, et. al. J Natl Compr Canc Netw. 2018 Nov;16(11):1362-1389. PMID: 30442736 Breast cancer risk reduction version 2.2015 Therese B Bevers, et. al. J Natl Compr Canc Netw. 2015 Jul;13(7):880-915. PMID: 26150582 NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 2.2021 Daly MB, et. al. J Natl Compr Canc Netw. 2021 Jan 6;19(1):77-102. PMID: 33406487

Type 2 Diabetes	Risk Category: **Polygenic Risk Care Recommendations** • Emphasize a healthy lifestyle: – Exercise regularly. – Maintain healthy body weight. – Eat a heart-healthy diet. • For adults and children 12 and older: – Assess for symptoms such as polyuria and weight change. – Consider a biochemical screen with hemoglobin A1c or fasting glucose. – If elevated hbA1c or fasting glucose: – Consider prescription of metformin. – Consider medical nutrition therapy consultation. **References:** American Diabetes Association 2021 Preventionhttps://diabetesjournals.org/care/article/44/Supplement_1/S34/30895/3-Prevention-or-Delay-of-Type-2-Diabetes-Standards

For any condition studied that is not listed in the table above, high risk was not identified. This means the polygenicrisk scores (PRS) for these conditions did not meet the threshold for high risk. For some conditions, other factorssuch as sequencing of specific genes (monogenic risk), or family history, also contributed to the risk estimate.Review the methodologies section for a full explanation of how high risk for each condition was determined.

Please note that a person's overall risk for any of these conditions could still be higher than the general population based on factors that are not included in the GIRA.

Information contained in this report does not replace evaluation by a health care provider. General risk reducingstrategies such as maintaining a healthy lifestyle and age recommended screening tests are still recommended.Questions about what this report means for this individual's medical management should be discussed with theirprovider.

Conditions not assessed:

Due to missing or incomplete data, risk was not able to be assessed for:

Coronary heart disease

GIRA Report

Risk Result:	**High Risk for Atrial Fibrillation**

Polygenic Risk: Not High

This individual's polygenic risk score was below the study threshold for high risk. See PRS report attached.

Monogenic Results: Positive

A pathogenic or likely pathogenic variant was identified in the LMNA gene. People with a pathogenic or likely pathogenic variant in the LMNA gene are at increased risk for heart and neuromuscular conditions, including arrythmia and cardiomyopathy. See Invitae report attached.

Family History: Positive

This patient reports a POSITIVE family history of atrial fibrillation. One or more parents developed atrial fibrillation before the age of 75. Affected family members can be found in the pedigree included in this GIRA report. We do not know how a positive family history combines with PRS in estimating risk for developing atrial fibrillation.

Clinical Factors: Not Evaluated

Clinical risk factors for this condition were not evaluated as part of this study.

Limitations of polygenic risk: This polygenic risk does not take into account the individual's non-genetic factors such as lifestyle, habits and historyof other diseases, which could affect risk. These results should be viewed in the context of the individual's medicalcare, family history, and racial/ethnic background. See the full methods and limitations for additional information.

GIRA Report

Risk Result:	**High Risk for Breast Cancer**

Monogenic Results: Negative

Gene sequencing did not identify any pathogenic or likely pathogenic variants related to this condition. See the Invitae report for a full list of genes sequenced.

Integrated Risk Score: High Risk

Based upon the participant's genetic risk, family history, and personal factors including age, sex, body mass index, breast density, reproductive history, and hormonal exposure, the lifetime risk of breast cancer to the age of 80 is 30%. The average woman has a lifetime risk of breast cancer of 12%, so this risk is higher.

Limitations of polygenic risk: This polygenic risk does not take into account the individual's non-genetic factors such as lifestyle, habits and historyof other diseases, which could affect risk. These results should be viewed in the context of the individual's medicalcare, family history, and racial/ethnic background. See the full methods and limitations for additional information.

GIRA Report

Risk Result:	**High Risk for Type 2 Diabetes**

Monogenic Results: Not Evaluated

No gene sequencing was completed for genes related to this phenotype.

Polygenic Risk: High Risk

A high polygenic risk score for type 2 diabetes was found in this individual. A high polygenic risk score is associated with 3-7 times increased risk for developing type 2 diabetes relative to a person not in the high risk category. The data is based on populations of African, European, East Asian and Hispanic/Latino descent. Information is insufficient or not available for populations of other descent.

Family History:

Family history provided by this participant did not meet the criteria for elevated risk. Family history may be incomplete or unknown.

Clinical Factors:

This patient has a history of one or more of the clinical risk factors listed below. Screening should be considered in overweight or obese adults who have one or more of the additional risk factors listed. Screening should also be considered for all adults over 45 years of age.

Risk Factor	Sub-Category	Present
Overweight or obese	BMI ≥ 25 kg/m2	Present
	Pediatrics: > 85%	Unknown
Demographics	Self-reported non-white race, non-Hispanic	Present
	Age ≥ 45	Yes
Diagnoses	Hypertension	Present
	Gestational Diabetes (female only)	Not Present
	Polycystic ovarian syndrome (female only)	Not Present
Lab tests	HDL < 35 mg/dL	Present
	Triglycerides >250 mg/dl	Not Present
	A1C ≥ 5.7%	Not Present

Limitations of polygenic risk: This polygenic risk does not take into account the individual's non-genetic factors such as lifestyle, habits and historyof other diseases, which could affect risk. These results should be viewed in the context of the individual's medicalcare, family history, and racial/ethnic background. See the full methods and limitations for additional information.

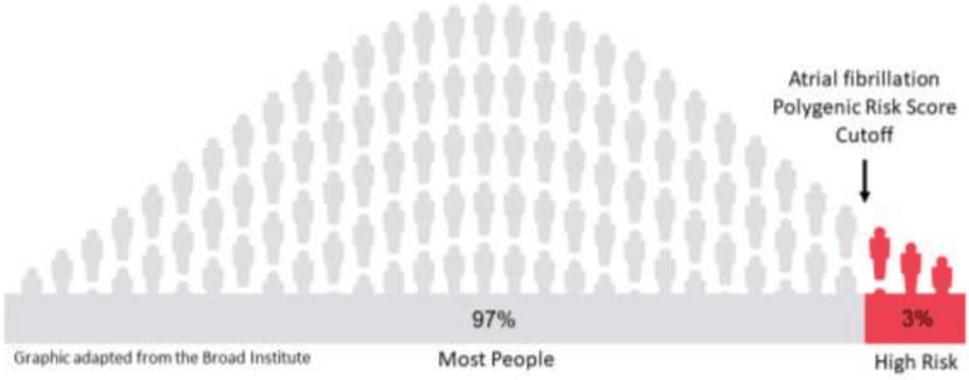
Atrial Fibrillation: Understanding Your Results

What is Atrial Fibrillation (also called "Afib")?

- Afib is an irregular heart rhythm or when the heart beats out of rhythm. Afib affects the top chambers of the heart (called the atria). The atria can beat faster than normal and make the heart beat in an irregular pattern going fast and then slow.
- Afib can be associated with feeling tired or short of breath, or it can have no symptoms at all. The heart can switch in and out of the Afib rhythm, and a person having this may have symptoms on and off or can have no symptoms at all. The risk of having a stroke is higher for people having Afib. The irregular heart beats can cause blood clots in the heart, which can become dislodged and cause a stroke.
- Afib is very treatable with medications and blood thinners. These treatments greatly reduce heart symptoms as well as the risk of stroke.
- Genetic and other factors like high blood pressure, obesity, sleep apnea and heart failure can lead to Afib.

What does high risk for Afib mean?

- On average, about 1 in 10 people, or 10% of people, over the age of 80 have AFib. The risk of Afib is less for younger people but people even in their 40's can have Afib.
- Your polygenic risk score (PRS) is in the top 3%. This means that you may have a higher genetic risk for Afib than 97 out of 100 people.



  - High risk for Afib means that your risk for developing Afib is about 2 times higher than a person not in the high risk category.
  - This does not mean that you have Afib or that you will definitely develop Afib in your lifetime.
- This PRS was created using genetic information from large research studies of people with European descent and validated in African American and Hispanic/Latino populations. We outline how this score was created below:
  - DNA differences were picked up that are linked to Afib risk
  - This score was tested using genetic information from other research studies with different populations and was accurate

        - This score was tested using genetic information from other research studies with different populations and was accurate. See the Broad PRS report attached.
    - Larger research studies are needed in people of other descents to provide a risk range for those populations - see the Broad PRS report attached.

What can you do to lower your risk for Afib?

- Not everyone who is at high risk for Afib will get it. Talk to your doctor(s) or healthcare provider about how to decrease your chances of getting Afib.
- We strongly recommend a healthy lifestyle, including no smoking, eating a healthy diet, and treating high cholesterol. There are specific lifestyle changes that can lower your risk for Afib:
    - Maintain a healthy weight
    - Participate in some form of exercise or physical activity for 30 minutes a day 4-5 times a week
    - Maintain a healthy blood pressure by taking your blood pressure and talking to your doctor if it is high
    - Treat sleep apnea if you have it or get screened for it if you think you have it. Symptoms include feeling tired in the day, excessive snoring, or disrupted breathing while sleeping.
    - Know if your blood sugar is elevated, which might suggest diabetes, and treat it if it is elevated
    - If you are at high risk, we will also talk to you about whether you want to participate in a study to wear a smart watch that can help detect if you are having Afib.

If you have heart palpitations that feel like skipped beats or irregular beats that last for a few minutes at a time, you should tell your doctor. If you have unusual dizzy spells or if you have passed out or almost passed out, you should tell your doctor. Even if you don't have symptoms like these, your doctor may want to record an electrocardiogram or have you wear a heart monitor to see your heart rhythm.

What are your next steps?

- If you are having the symptoms above, you should contact your doctor.
- You should share these results with your doctor(s) or other healthcare provider to discuss actions to be taken to lower your risk.
- You may also want to share your results with your family members.
- Your results will be uploaded to your electronic health record for you to review and will be available to your doctor(s) and other healthcare providers.
- If you have any questions about your results, please contact the study team at your institution. You can find this contact information on the cover page of the GIRA.

Breast Cancer: Understanding Your Results

What is breast cancer?

- Cancer is a disease in which cells in the body grow out of control. When cancer starts in the breast, it is called breast cancer. Although many types of breast cancer can cause a lump in the breast, not all do. Breast cancer can spread when the cancer cells get into the blood or lymph system and are carried to other parts of the body.
- Risk factors for breast cancer include variants in your genes, having other family members with breast cancer (family history), and your age. Your reproductive history can affect your risk for breast cancer. This includes how many children you have had, whether you breast-fed your children, and when you started and stopped having your period. There are also lifestyle factors that affect an individual's risk for breast cancer including use of hormonal birth control, estrogen replacement therapy, weight and how much alcohol you drink.
- You can learn more about breast cancer and risk factors here (https://www.cancer.org/cancer/breast-cancer/about.html)

What does high risk for breast cancer mean?

- On average, 12-13 out of 100 women, about 12-13% of women, will get breast cancer in their lifetime, by the age of 80 years.
- High risk for breast cancer means that you have a risk of getting breast cancer of 25 or more out of 100, or 25% or greater in your lifetime, by the age 80 years. *Please see your test report for more information about your specific lifetime risk for breast cancer.*

This picture shows high risk for breast cancer. 25 women* (red) get breast cancer and 75 women (gray) do not.

This picture shows overall high risk for breast cancer. *Your risk may be the same as this or higher.* Please look at your test report for your specific risk.

*Women here refers to individuals assigned a female sex at birth.

- The breast cancer risk score is integrated, meaning it takes multiple sources of risk into account. The integrated risk score includes genetic factors such as polygenic risk and family history and non-genetic factors such as reproductive history, medicine that affect hormone levels, weight and age. This integrated score included genetic information from large research studies of people with European, East Asian, African, and Hispanic/Latino descent.

What can you do to lower your risk or detect breast cancer early?

- Not everyone who is at high risk for breast cancer will get it.
- Early breast cancer detection:
  - Continue or start to perform monthly breast self-exams ((https://www.breastcancer.org/symptoms/testing/types/self_exam). This is important to help you know your own breasts and notice any changes as soon as possible. You should talk to your doctor if you notice any changes.
  - For women at high risk for breast cancer, we suggest alternating mammogram and breast MRI every 6 months, beginning at age 40 or 10 years younger than the youngest family member's breast cancer diagnosis, whichever is younger.
- To lower your risk:
  - Talk to your doctor about estrogen-blocking medications like tamoxifen.
  - Talk to your doctor about avoiding medications containing estrogen.
  - Consider breast feeding if appropriate.
  - Maintain a healthy body weight with a body mass index (BMI) (https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html) < 25, eat a healthy diet, keep physically active and limit alcohol intake.
  - Surgical removal of healthy breasts is typically not recommended, but discuss this with your doctor if you have concerns.

What are your next steps?

- You should share these results with your doctor(s) or other healthcare provider to discuss actions to lower your risk.
- You may also want to share your results with your family members.
- Your results will be uploaded to your electronic health record for you to review and will be available to your doctor(s) and other healthcare providers.
- If you have any questions about your results, please contact the study team at your institution. You can find this contact information on the cover page of the GIRA.

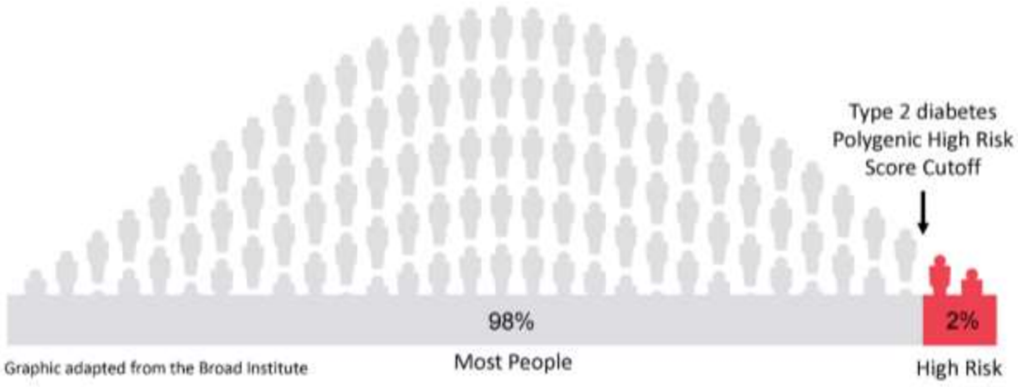
Type 2 Diabetes: Understanding Your Results

What is Type 2 Diabetes?

- Type 2 diabetes is a condition where the level of sugar (glucose) in your blood is too high.
- Your blood always has some sugar in it, but too much sugar isn't good for your health.
- If your blood sugar level remains high over time, it can cause serious damage to your heart, eyes, kidneys, and feet.
- Genetic and lifestyle factors like too little exercise, poor diet and obesity can lead to type 2 diabetes. Risk for developing type 2 diabetes increases with age.

What does high risk for type 2 diabetes mean?

- Your polygenic risk score (PRS) is in the top 2%. This means that you may have a higher risk for type 2 diabetes than 98 out of 100 people.



- On average, 1 in 10 people, or 10%, will get type 2 diabetes in their lifetime. High risk for type 2 diabetes means that your genetic risk is 3-7 times higher for developing type 2 diabetes compared to a person not in the high risk category.
- This result does <u>not</u> mean that you have type 2 diabetes or that you will definitely develop in your lifetime.
- This PRS was created using genetic information from large research studies of people with European, Asian, African, and Hispanic/Latino descent. We outline how this score was created below:
  - DNA differences in each population were picked up that are linked to type 2 diabetes risk
  - This score was tested using genetic information from other research studies with different populations and was accurate
- Larger research studies are needed in people of other descents to provide risk ranges for other populations - see the Broad PRS report attached.

What can you do to lower your risk for type 2 diabetes?

- Not everyone who is at high risk for type 2 diabetes will get it. Talk to your healthcare provider about how to decrease your chances of getting type 2 diabetes. You can lower your risk by:
  - Eating healthy foods, including fruits and vegetables, nuts and whole grains
  - Keeping your weight in a healthy range
  - Aiming for 30 minutes a day of moderate exercise, such as brisk walking or bicycling, at least 5 days a week
- Your doctor may order a blood or urine test to screen for diabetes. Start diabetes screening at age 45, or earlier if you are overweight and:
  - You are African American, Hispanic/Latino, Native American, Asian American or Pacific Islander
  - Your mother, father, sibling or child has type 2 diabetes
  - You were diagnosed with hypertension or heart disease
  - You have a lab test that shows low HDL cholesterol (good cholesterol) or high triglycerides
  - You do not exercise often
  - You are a woman with
    - Polycystic ovary syndrome
    - A history of gestational diabetes or are pregnant
- Discuss medications and other treatments with your doctor or other healthcare provider.

What are your next steps?

- You should share these results with your doctor(s) or other healthcare provider to discuss actions to be taken to lower your risk.
- You may also want to share your results with your family members.
- Your results will be uploaded to your electronic health record for you to review and will be available to your doctor(s) and other healthcare providers.
- If you have any questions about your results, please contact the study team at your institution. You can find this contact information on the cover page of the GIRA.

Frequently Asked Questions

What is the Genome Informed Risk Assessment (GIRA) or health risk report?

The Genome Informed Risk Assessment (GIRA) is the overall report from this research study. This report says if you/your child are at high risk for any of the health conditions studied. "High risk" means that you have a higher chance of getting a condition than the average person. This study looked at 9 conditions for adults and 4 conditions for children under 18.

Health Conditions Assessed	
Asthma (children)	Hypercholesterolemia (adults)
Atrial Fibrillation (adults)	Obesity (children and adults)
Breast Cancer (adults)	Prostate Cancer (adults)
Chronic Kidney Disease (adults)	Type 1 Diabetes (children)
Colorectal Cancer (adults)	Type 2 Diabetes (children and adults)
Coronary Heart Disease (adults)	

This report has information about health risks including genetic (one or more genes), you/your child's health history, and family health history. If you were found to be at high risk for one or more conditions, you can learn more about your risk in the "Understanding Your Risk" pages. You can speak to a study staff member about your results. This report may be put in your electronic health record and will be given to your doctor. It contains a summary of your risk factors, as well as the gene reports and family history information described in the consent form.

What is monogenic risk?

A single difference in one gene can have a big impact on a person's risk for developing a health condition. This is called monogenic risk because "mono" means "one." For adults in this study, your health risk report includes genetic testing results for a small number of monogenic risks. Children in this study were not tested for monogenic risks. You should talk to your doctor about your results from this study. Your doctor may recommend changes in your healthcare.

What is a Polygenic Risk Score (PRS)?

Everyone has thousands of genetic differences. Some genetic differences can slightly increase the risk for developing a health condition. A polygenic risk score (PRS) is made by adding up these small genetic risks. It is called polygenic risk because "poly" means "many." A PRS is used to estimate the overall risk someone has of developing a health condition. PRS is a new method for estimating risk. Scientists are still working to improve PRS for different conditions. This study is

trying to see if these risk estimates are helpful for you and your doctor(s). You should talk to your doctor about your results from this study. Your doctor may recommend changes in your healthcare.

How should I talk to my doctor about my results?

You should share this report with your doctor. You should ask your doctor what the results mean for your health. You should ask your doctor to help you follow any recommendations made in the report.

What are the possible results for each condition?

You can receive two types of results for each condition tested. These results will either be 'high risk' for a condition OR 'not at high risk' for a condition.

- You can be 'high risk' for the following reasons:
  - You had a positive monogenic result. A positive monogenic result means a genetic difference in one of your genes that is known to increase risk was found. OR
  - Your PRS was above the study threshold for a condition. The study "threshold" is the point at which someone's risk for developing a condition is higher than the average person. OR
  - You have one or more close family members with the condition.
- You can be 'not at high risk' for the following reasons:
  - You had a negative monogenic result. A negative monogenic result means no genetic differences that increase risk were found. AND
  - Your PRS was below the study threshold for a condition. The study "threshold" is the point at which someone's risk for developing a condition is higher than the average person. In this study, the researchers set a specific threshold to indicate high risk that is unique to each condition. OR
  - You did not have a strong family history for the condition.

How accurate are these results?

The GIRA health risk report gives a summary of many different types of risk factors. The accuracy of your family history risk depends on how much information you knew about your relatives. The accuracy of your clinical risk factors depends on responses to the surveys and information from your electronic health record. Your genetic risk is made up of monogenic and polygenic tests. Monogenic tests have been around for a long time and have clear recommendation guidelines. Your polygenic risk score results are based on what science currently knows about genetic differences that impact a person's risk for these conditions. The GIRA health risk report is not diagnostic. This research study measures *risk (or the chance) of developing a health condition*. Scientists cannot know for sure who will develop a disease and who will not. Health conditions can have multiple causes.

Genetic research studies need a large number of diverse participants to answer questions about our genes. Many polygenic risk scores were developed using data mostly from people of European descent. The study PRSs may not be as good at estimating risk in people who are not of European descent. This study tried to make PRSs that used genetic information from people of many different races, ethnicities, or ancestries. Where possible, the results have been validated (or confirmed) in people from four populations: Asian descent, African descent, European descent, and Hispanic/Latino descent. However, this type of information was not always available for every condition. This may impact how well your results estimate your risk for the health conditions. Please refer to the methods section to learn more about how this limitation may impact your results.

You may identify with more than one, none, or all of the listed populations. Across the different results you receive in your GIRA, some may still be meaningful even if you don't identify with the populations mentioned. You should discuss all of the results you receive with your doctor. Your risk likely falls within the range of risk presented in the report. Your participation in this study may help improve health care for all people in the future.

What does it mean if I am at high risk for one or more conditions?

Being at high risk for one or more conditions means you are in the top 2-10% of the population for developing a condition based on your polygenic risk score. This means you have a higher chance of developing that health condition than the average person, but does not mean you will definitely develop the condition. You may be at high risk due to your genetic results or family history. The "Understanding Your Results" pages in this report will help you understand what your high risk results mean for your health and your medical care.

What does it mean if I am not high risk?

Being defined by the study as not high risk does not mean you are at low risk for developing that condition. Your overall risk for any of these conditions could still be higher than the average person based on factors that were not looked at in this study.

What if I already have one of the conditions studied and I am found to be at high risk?

There are many causes that can lead to developing a health condition. Other aspects of life such as lifestyle, environment, random chance, or other genetic differences not studied may be part of why you were diagnosed with the health condition.

What if I already have one of the conditions studied and I am not given a high risk result?

There are many reasons that someone develops a health condition. This research study measures risk from certain causes (such as your genetics and family history). Sometimes people who do not have any risk factors will still develop disease. Lifestyle, environment, random chance, or other

genetic differences not studied may be part of why you were diagnosed with your health condition.

What do these results mean for my family?

Monogenic risk has been studied for a longer time and we have more information about these genes. We know that your monogenic risk is important information for your blood relatives to know. PRSs are new and are still being studied. We do not currently know what your PRS results mean for your blood relatives. You should talk with your family members and they should discuss your family medical history and your test results with their own doctor(s).

Could my results change?

Your genes do not change, but science does. New tools to estimate risk could become available. The interpretation of your genetic differences could change. These research results were generated using the most up to date knowledge and information available at the time this report was written.

What other factors might influence my risk that are not accounted for?

This report is based on what we currently know about genetic differences that impact a person's risk for the conditions tested in this study. However, there are many factors that influence risk. Some of these factors are understood by scientists and doctors, but there are many factors that are still unknown. Some factors change over time like a person's age, lifestyle, environment, medications, or diet and their risk for disease can change as well. People can have genetic differences that have a small or large impact on risk. Not all genetic differences that influence risk for disease were tested in this study. Family history and clinical risks factors were evaluated based on the information available. If any of the information used to estimate risk was missing, your risk estimate may not be as good. Children were only tested for a few of the conditions included in this study. A list of the conditions tested can be found on the first page of this report. Please refer to the methods section to help understand how the risk estimates apply to you.

About this study

The genome integrated risk assessment (GIRA) was developed as part of a research study by the Electronic Medical Records and Genomic (eMERGE) network and funded through the National Institute of Health (NIH). This study was approved by the central institutional review board at Vanderbilt University Medical Center (IRB 211043).

Methods

Monogenic sequencing:
Sequencing for monogenic variants in 16 genes was performed by Invitae, a CLIA accredited laboratory. This custom proactive panel test includes the following genes: *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, APOB, LDLR, LDLRAP1, PCSK9, PALB2, PTEN, STK11, TP53, LMNA*. See the Invitae report attached for a description of methods.

Polygenic risk calculation:
Genotyping was performed at the Broad Institute using the CLIA accredited Global Diversity Array from Illumina, Inc. Polygenic risk scores for each condition were calculated from the genotyping data. See the attached Broad eMERGE Polygenic Risk Report for a description of methods.

Family History:
Family history information was self-reported by the participant or their parent/caregiver using MeTree software developed by the Duke Center for Applied Genomics and Precision Medicine. The participant's pedigree was generated using MeTree.

Clinical data:
Clinical data used in this study were obtained from the participant's electronic health record with participant/parent consent or from self-report via participant/parent/caregiver completed surveys. Clinical data, along with genetic data, was used to estimate risks for breast cancer and coronary heart disease as part of integrated risk scores. Clinical data for other conditions may be displayed for provider reference.

Care Recommendations:
Care recommendations were generated by members of the eMERGE network and represent the collective recommendations of disease experts, clinical care providers, and researchers.

Integrated Scores:
Breast cancer: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (https://ccge.medschl.cam.ac.uk/boadicea/) predicts breast cancer risk based upon the family history, lifestyle/hormonal risk factors, rare pathogenic variants in moderate and high risk breast/ovarian cancer susceptibility genes, and a polygenic risk score calculated using >300 single-nucleotide variants that explain ~20% of breast cancer polygenic variance. At present, BOADICEA has only been validated for women of European ancestry and might not be as accurate in other populations. The baseline (population) incidence is chosen according to the report by the Centers for Disease Control and Prevention and National Cancer Institute in 2020.

Coronary heart disease: The Pooled Cohort Equation (PCE) is an established tool used to estimate 10-year risk of coronary heart disease events, such as myocardial infarction, using demographic and clinical risk factors. These factors include age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, hypertension treatment, current smoking status, diabetes diagnosis (PCE cannot be estimated if any of these factors are missing). The PCE was combined with polygenic risk to generate an integrated score for CHD. The PCE is validated in those aged 40+ and in White and African American populations. The PCE is not valid for those under the age of 40 and may not be as accurate in other populations. Risk associated with monogenic familial hypercholesterolemia (*LDLR, APOB, PCSK9,* and *LDLRAP1*) and family history of CHD are not accounted for in the PCE risk estimate. For more information on the PCE, please see reference: https://www.jacc.org/doi/pdf/10.1016/j.jacc.2013.11.005

GIRA Generation:
Determination of high risk for each condition evaluated was disease specific. See the tables below for the criteria used to determine high risk for each condition:

Table 1: Conditions evaluated in adult participants aged 18+ at time of enrollment.

Condition	Age range assessed	PRS used to calculate risk	Genes Sequenced	Family History used to determine high risk	Integrated score using clinical data and PRS
Atrial fibrillation	18+	Yes	*LMNA*	No	No
Breast cancer	18+	Yes	*BRCA1, BRCA2, PALB2, PTEN, TP53, STK11*	Yes	BOADICEA (see methods)
Chronic kidney disease	18+	Yes	None	Yes	No
Colorectal cancer	18+	No	*EPCAM, MLH1, MSH2, MSH6, PMS2, STK11, PTEN, TP53*	No	No
Coronary heart disease	18+	Yes	*APOB, LDLR, LDLRAP1, PCSK9*	Yes	Pooled cohort equation (see methods)
Hypercholesterolemia	18+	Yes	*APOB, LDLR, LDLRAP1, PCSK9*	No	No
Obesity/BMI	3+	Yes	None	No	No
Prostate cancer	18+	Yes	*BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2*	Yes	No
Type 2 diabetes	3+	Yes	None	No	No

Table 2: Conditions evaluated in pediatric participants aged 3-17 at time of enrollment.

Condition	Age range assessed	PRS used to calculate risk	Genes Sequenced	Family History used to determine high risk	Integrated score using clinical data and PRS
Asthma	3-17	Yes	None	No	No
Obesity/BMI	3+	Yes	None	No	No
Type 1 diabetes	3-17	Yes	None	No	No
Type 2 diabetes	3+	Yes	None	No	No

Limitations

Genetic research studies need large numbers of participants to understand how human DNA (or genes) contributes to disease risk. When research studies have low representation of some races, ethnicities, or ancestries (populations of descent), there is less genetic information available to understand risks for people in those groups. The GIRA health risk report has been validated (or confirmed) in up to four populations: Asian descent, African descent, European descent, or Hispanic/Latino descent. The report will name the populations included in the validation process. The estimate of risk may not be as accurate for some conditions if the participant is from a population that was not included in the validation process.

LIMITATIONS OF POLYGENIC RISK SCORES

Polygenic risk scores do not consider an individual's non-genetic factors such as lifestyle habits and personal or family medical history, which could affect risk. This research study used polygenic risk scores that were derived from people from several different populations. However, this type of information was not always available for every population. Although polygenic risk scores may be associated with disease risk in all populations, the scores are generally more accurate in people of European descent.

LIMITATIONS OF GENE SEQUENCING

All genetic tests have limitations. Some types of genetic variants may not be found by the gene sequencing test performed by Invitae. This means the test may rarely give an inaccurate result. If other family members are also tested, the Invitae test may find that family relationships are not what the participant believes them to be. Invitae will only report these findings if necessary to provide correct test results.

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