Instructions: Complete this template to provide IRB members and designated reviewers with sufficient information to conduct a substantive review of human research. If applicable, submit a Sponsor's Protocol in addition to this document. Detailed instructions for preparing this template can be found in the Investigator's Manual. If the proposed human research is eligible for an Exemption Determination, see Appendix H of the Investigator Manual.

GENERAL INFORMATION	
Protocol/ESTR Record Number (if assigned): IRB19-0594	
Version Number: 13	**Version Date: 6/10/2021**
Principal Investigator: Jason Vassy, MD, MPH	
Principal Investigator's Harvard Affiliation: Faculty	
Protocol Title: Pragmatic randomized trial of polygenic risk scoring for common diseases in primary care	

1. Specific Aims

One of the most pressing controversies in genomics today is the clinical utility of polygenic risk scores (PRS). Broadening the scope of genomic risk testing beyond monogenic diseases, PRS combine information from hundreds or even millions of genetic loci, each with a very small effect size on the risk of common complex disease1-6. The result is a continuous quantitative risk factor for susceptibility to conditions such as coronary artery disease (CAD), type 2 diabetes (T2D), and breast cancer7. Compared to rarer monogenic disease variants, PRS have greater transformative potential for public health and healthcare in their ability to identify much larger proportions of the population at significantly elevated risk for disease, facilitating evidence-based prevention and management8-10. Moreover, their prediction ability has vastly improved compared to earlier PRS that included only a limited number of genetic variants7,11,12. However, while the associations between PRS and a wide range of common diseases are well established (clinical validity), the potential impact of this information on patient health outcomes (clinical utility) remains contested and understudied. Proponents argue that, because PRS in the upper tails of the distribution confer an equivalent risk to rare variants associated with monogenic forms of disease, they should similarly impact clinical screening and prevention strategies5,7. Opponents argue that PRS are poorly calibrated for populations outside the cohorts used for their development and validation, including different ancestral groups, and that they achieve similar discrimination for disease risk as other risk factors already used in clinical care (e.g. body-mass index and smoking) or readily available without additional testing (e.g. socioeconomic status)13-16. Nonetheless, the invariability of PRS over the entire life course and the possibility of deriving PRS for multiple conditions from a single, relatively inexpensive test make them attractive candidates for novel risk factors in an era of increasing access to genotyping6, and laboratories and healthcare system in the US and abroad are racing to bring PRS to patient care14. Despite disagreement about the readiness of PRS for clinical use, there is more agreement that patient outcomes data are needed to demonstrate their clinical utility, ideally prospectively collected from real-world medical practice17-19. It is also recognized that PRS alone will be insufficient to achieve improvements in patient health, if they lack actionability to facilitate their use by frontline healthcare primary care providers (PCPs) with variable genetic literacy4,13,17.

In this project, we will extend our innovative point-of-care pragmatic trial methodology to examine effectiveness and implementation outcomes from the use of PRS for 6 common diseases that are

screened for by PCPs and have established prevention strategies: CAD, atrial fibrillation (AFib), T2D, colorectal cancer, prostate cancer, and breast cancer. In this project, we will:

1. Conduct a randomized controlled trial (RCT) to determine the clinical effectiveness of PRS among patients
at high genetic risk for at least one disease, measured by changes in clinical management (process outcomes) and time to diagnosis of prevalent or incident disease (clinical outcome) over 24 months.

> Primary hypothesis: Time-to-new-diagnosis of one of 6 common complex diseases will be lower in patients undergoing PRS compared to patients undergoing usual care (UC) 24 month after randomization

2. Measure high-priority genomic medicine implementation outcomes, including PCP knowledge and beliefs about PRS, patient activation in healthcare, medication adherence, and costs.

2. Background and Significance

2.1 Provide the scientific background and rationale for the research.

PRS exemplify the disparity between clinical validity and utility that plagues much of genomic discovery. Increasingly large genome-wide association studies (GWAS) continue to identify new loci associated with common disease20-30, and large independent cohorts are increasingly available to replicate the performance characteristics of GWAS-derived PRS for disease associations6,7,20,21,31. For some diseases, PRS have now achieved area-under-the-curve (AUC) values of 0.7 or higher, similar to risk predictors already used clinically7,15,16. A recent study by Khera showed that PRS for 5 common diseases, calculated from up to 6.9M variants and their GWAS-derived effect estimates, achieved higher AUC than PRS consisting of only dozens or hundreds of GWAS-significant variants7. This and other work have reignited interest among genomics researchers in using PRS to identify high-risk individuals and enable precision preventive medicine14. However, early applications of PRS to clinical care have been largely unsuccessful in improving patient outcomes. Early RCTs, including ours32,33, have tested the hypothesis that PRS for conditions such as CAD and T2D can motivate patient health behavior changes34-37. A recent meta-analysis of such trials found that communicating PRS and other DNA-based risk estimates did not improve behaviors such as smoking cessation, diet, or medication use37, consistent with evidence outside genomics that risk communication alone is generally ineffective in improving health behaviors38,39. Even if newer PRS achieve higher predictive ability than their earlier counterparts, translating risk information into improved outcomes will remain challenging. In many of these studies, the missing links between PRS and clinical benefit is the involvement of healthcare providers and the "actionability" of the risk results, namely, specific recommendations for how the results should change clinical management. The recent MI-GENES RCT by Kullo gives evidence that provider involvement might help translate PRS results into improved clinical outcomes23,40. An intervention that delivered both a CAD PRS and a shared decision-making tool to patients and physicians resulted in greater statin use and lower cholesterol after 6 months than the tool alone.

2.2 Describe the significance of the research, and how it will contribute to generalizable knowledge.

Despite the rapid pace of genomic discovery in the last 20 years, the clinical translation of these discoveries to improve patient outcomes has lagged17,41. Several challenges remain in bringing genomics to the clinic. Chief among these is the absence of conclusive improvements in patient outcomes from many genomic interventions17,18,42. The overall vision for this proposal is to conduct outcomes research to measure the utility of genomic medicine interventions in real-world medical practice. Generalizing from our framework for the clinical utility of pharmacogenetic testing43, the conceptual framework for this proposal posits that genetic/genomic information might act through both patients and providers to effect improved outcomes but is unlikely to do so if not linked to specific actionable recommendations, such as appropriate diagnostic testing, screening paradigms, or targeted therapy.

This project will use key strategies to generate evidence for the utility of genomic information:

● Large clinical databases and robust electronic health record (EHR) systems enable integrated healthcare systems to generate rigorous, cost-efficient, and generalizable evidence to study and support the use of genomic medicine interventions in practice44. Their organizational structures enable both horizontal and top-down diffusion and implementation of ideas and interventions.
● Pragmatic RCT designs enable the generation of rigorous evidence with enhanced generalizability45. One strategy to promote pragmatic design is to embed genomic medicine interventions into existing clinical workflows, including point-of-care provider and patient enrollment and data collection.
● Delivering genomic results coupled to established evidence-based screening and prevention strategies, to both patients and providers, can provide the synergy and actionability needed to impact healthcare and health outcomes, succeeding where prior trials of genomic medicine have failed37,39.
● Trial outcomes should be chosen for their relevance to patients and other healthcare stakeholders18,46-48.
● Implementation science can help researchers and stakeholders identify and address reasons for the common and frustrating failure to implement biomedical interventions shown to be effective in RCTs49-51.
● Dissemination of research findings to relevant stakeholders at local and national levels, with a focus on non-genetics professionals, is critical to maximizing their reach17,52,53.

The scalable framework we develop in this proposal will generate critical generalizable evidence about the clinical utility of PRS. The pragmatic point-of-care trial platform is also readily adaptable for the rigorous yet pragmatic examination of other genomic medicine interventions.

3. Research Locations and Collaborating Sites

3.1. Where will the research activities take place? (check all that apply)

☒ **At Harvard: Harvard Medical School**
☒ **At another location in Massachusetts: VA Boston Healthcare System (VABHS)**
☐ **In another state in the U.S.**
☐ **Internationally**

3.2. Describe the sites or locations where the research will be conducted or overseen by the Harvard PI.

Dr. Vassy will oversee the research activities at the VA Boston Healthcare System and Harvard Medical School.

3.3. Describe plans for communication among sites regarding adverse events, interim results, protocol modifications, monitoring of data, etc. ☐ N/A.

Adverse events (AE) are defined in Section 18 below. Study staff will report all deaths and study-related AEs, protocol deviations, and unanticipated problems to the IRBs at both HMS and VABHS concurrently. There are otherwise no plans for reporting interim results. Similarly, protocol, study staff, and other amendments will be submitted to the IRBs at both HMS and VABHS concurrently.

3.4. Describe any local (international or state) laws, regulations, and/or customs affecting the research (e.g., age of majority, mandatory reporting requirements, etc). ☒ N/A.

3.5. Identify any approvals or permissions required of collaborating institutions, community leaders, or government officials, including approval from another IRB or local research ethics committee. ☐ N/A.

Approval from the VABHS IRB and Research and Development (R&D) committees is also needed and is pending.

3.6. Will you collaborate with any researchers not affiliated with Harvard to carry out this study?
☐**No** ☒**Yes:** Yes, with the VABHS – however all VA researchers will be covered by the VA IRB approval.

3.7. Will your collaborators interact with human subjects, have access to identifiable data/specimens, and/or be responsible for the design, conduct, oversight, or reporting of the research?
☐**No** ☒**Yes:** All collaborators will be covered by the Harvard and/or VA Boston IRB's.

3.8. Will any institution conducting research activities as part of this study, including collaborators, rely on Harvard LMA for IRB review?
☒**No** ☐**Yes:**

4. Study Team

4.1. Describe the Principal Investigator's experience conducting research at the study site(s) and familiarity with the local research context.

Dr. Vassy is the PI of the Integrating Pharmacogenetic in Clinical Care (I-PICC Study) and has recently completed enrollment of 400 patients into this pragmatic randomized trial of pharmacogenetic testing at VABHS, the setting in which the current research will take place. He is also the VABHS site PI for the PRIME Care Study trial of pharmacogenetic testing for the treatment of major depression.

4.2. Describe how the Principal Investigator will ensure that sufficient time is devoted to conducting and completing the research.

The grant funding for this research will support 6 calendar-months of Dr. Vassy's effort for the first year and at least 3.6 calendar-months of effort for the remaining 4 years, providing adequate time for him to devote to conducting the research.

4.3. Describe how all research staff members are trained to ensure that they are adequately informed about the protocol and study-related duties.

All research staff will maintain CITI certification during their entire participation in the research. The research protocol and staff-related duties will be discussed at weekly study meetings.

4.4. Describe the minimum qualifications for each research role (e.g., RN, social worker, phlebotomist, statistician), their experience in conducting research, and their knowledge of the local research context.

Investigators: Drs. Vassy and Lebo have experience developing comprehensible genetic and genomic reports, including those with PRS results. In the MedSeq Project, Lebo and Vassy were on the team that developed CLIA-certified PRS from Illumina HiSeq genome sequence data for 8 cardiometabolic traits, including CAD, AFib, and T2D[54,55]. Patients' PRS results were delivered directly to physicians in a comprehensive Genome Report and represented as polygenic relative risks (e.g. "1.3") and percentile ranks (e.g. "70-80th percentile")[55-58]. In the present study, Vassy and Lebo will refine the messaging delivered to participants and their PCPs about the PRS results on the PRS reports. Each report will state the disease(s) for which $OR_{PRS}>2.0$, the percentile for the $OR_{PRS}>2.0$, and the estimated absolute disease risk based on the PRS and established risk models or national incidence data[93-96]. The reports will also state limitations, including that most risk prediction research has been done in European ancestry individuals and thus there is more uncertainty in risk prediction among other racial/ethnic groups. Vassy and Lebo have experience developing clear clinical genetic/genomic reports and associated materials both for patients and their physicians[32,33,57,68-71]. From the MedSeq Project, we know that patients experienced no distress upon receiving polygenic risk information related to their risk of common diseases, and their PCPs were generally able to discuss the information with them appropriately[70].

Project manager (TBD): He/she has experience organizing and managing a research project, under the direction of the PI. He/she schedules study meetings, prepares agendas, materials, and minutes, and is the primary point-of-contact between the research team and the IRB and other regulatory bodies. He/she has experience interacting with patients and providers at the VA Boston Healthcare System for research-related activities.

Research assistant (TBD): He/she has experience interacting with patients and providers at the VA Boston Healthcare System for research-related activities. Under the direction of the PI and project manager, he/she can contact participants to administer surveys per protocol and schedule study visits.

Genetic counselor (TBD): He/she is a board-eligible/board-certified genetic counselor with experience communicating genetic results to patients in clinical settings and participants in research settings.

He/she contacts study participants found to have incidental clinically actionable genetic variants, delivers genetic counseling about these results, and facilitates connecting the participant to appropriate clinical follow-up.

5. Study Design

5.1. Describe the study design type.

Pragmatic randomized controlled trial.

5.2. Does the study involve more than one participant group?

☒. **Any participant with an actionable genetic variant will be withdrawn from the RCT portion of the study and will instead be followed along with the concurrent control group, although their data will not be analyzed with the concurrent control group.**

5.3. Indicate the duration of a participant's involvement.

Approximately 24 months

5.4. Indicate the total number of participants to be screened (if applicable) and/or enrolled (i.e., signed consent form). If the proposed research involves secondary data analyses only, indicate the number of data, documents, records, and/or specimens that will be obtained.

The structured electronic health record data of up to 50,000 patients in the VA Boston Healthcare System will be screen for eligibility. Patients meeting eligibility criteria will be recruited by study staff with the target of enrolling 1,076.

5.5. List inclusion and exclusion criteria, including age ranges of all participants, and describe the screening process.

Any patient receiving primary care at VABHS meeting the following criteria will be eligible for participation:

Inclusion criteria:

1) Age 50-70 years at enrollment
2) No known diagnosis of the following conditions, initially screened by the International Classification of Disease (ICD) codes or other EHR data using validated methods and then confirmed with potential patient-participants during recruitment:
a) Coronary artery disease: ICD-9 Codes 410-414 or ICD-10 Codes I20-I25 or ICD-9 Procedure Codes 36, 00.66 or CPT Codes 33510-33536, 9292x, 9293x, 9294x, 92973, 92974, 92975
b) Atrial fibrillation: ICD-9 Codes 427.3 or ICD-10 Codes I48 or ICD-9 Procedure Codes 37.33, 37.34
c) Type 2 diabetes: ICD-9 Codes 250 or ICD-10 Codes E10-E11, E13 or use of medication to treat diabetes mellitus

d) Colorectal cancer: ICD-9 Codes 153, 154.0, 154.1, 159.0, 230.3, 230.4, V10.05, V10.06 or ICD-10 Codes C18, C19, C20, C26, D01.0, D01.1, D01.2, Z85.038, Z85.048 or ICD-9 Procedure Codes 17.31-17.36, 45.71-45.76, 45.81-45.83 or CPT Codes 44140-44160, 44204-44212
e) Breast cancer: ICD-9 Codes 174, 175, 233.0, V10.3 and ICD-10 Codes C50 - C50.9, D05, Z853 or ICD-9 Procedure Codes 85.20, 85.21, 40.22, 40.23, 85.22, 85.23, 85.33-85.36, 85.41-85.48 or CPT Codes 19120, 19125, 19126, 19160, 19162, 19180, 19182, 19200, 19220, 19240, 19300-19307
f) Prostate cancer: ICD-9 Codes 185, 233.4, V10.46 and ICD-10 Codes C61, D07.5, Z85.46 or ICD-9 Procedures Codes 60.21, 60.29, 60.3, 60.4, 60.5, 60.62, 60.69 or CPT codes 55801, 55810, 55812, 55815, 55821, 55831, 55840, 55842, 55845

There are no other exclusion criteria for this study.

5.6. Describe study procedures.

i. Identification of eligible patients:
Study staff perform a regular query of the VA Corporate Data Warehouse (CDW) to generate patient eligibility tables. This query assesses potential eligibility: age 50-70 years and absence of the ICD codes and other data indicating an established diagnosis of one of the 6 target diseases. Patient eligibility is further confirmed by review of the patient's electronic medical records (Computerized Patient Record System, CPRS).

ii. Patient recruitment:
Study staff mail recruitment materials to potentially eligible patients. This mailing includes a recruitment letter (see "GenoVA Recruitment Letter") and a pre-stamped, self-addressed postcard with a coded study participant ID giving the patients the ability to opt-out (see "GenoVA Opt-Out Postcard"). After at least ten days, study staff follow each letter with a telephone call to the potential participant to confirm interest in participating in the study and screen for eligibility (see "GenoVA Telephone Scripts"). If the patient confirms interest and is found to be eligible to participate in the study, study staff then sends a second mailing. This mailing includes a cover letter (see "GenoVA Cover Letter"), a combined Informed Consent and HIPAA Authorization form (see "GenoVA Informed Consent Form and HIPAA Authorization"), an Authorization to Release Health Information form (VA Form 10-5345) if participant opts to have results information sent to non-VA provider, and a pre-stamped, self-addressed envelope the patient will use to return the signed combined Informed Consent and HIPAA Authorization form. After at least 10 days, study staff will call the patient to review the combined Informed Consent and HIPAA Authorization form, answer any questions, obtain consent to enroll in the study, and ask the participant to sign and date the combined Informed Consent and HIPAA authorization form (and, if applicable, VA form 10-5345) and return by mail in an included stamped envelope (see "GenoVA Telephone Scripts").

After the initial contact by standard mail and the opportunity to opt out of contact, patient-participants have the option to request that study staff send recruitment and other study materials (i.e. cover letter, combined Informed Consent and HIPAA Authorization Form, and VA Form 10-5345) via Azure RMS encrypted e-mail, DocuSign envelope (Azure RMS encrypted e-mail containing links to study documents for patient-participants to review and sign after study staff have obtained verbal consent), or, alternatively, may schedule a remote visit via phone or video call with study staff. VA-approved technologies such as Webex, VA Video Connect (VVC), and Doximity will be used to conduct video

calls with prospective participants. Before the remote visit, a copy of the combined Informed Consent and HIPAA authorization form, and, if applicable, VA Form 10-5345 will be sent to the prospective participant for their review. To help ensure that the forms are signed properly, signature lines will be flagged with an "X," and/or highlighted. After the consent information is reviewed with the prospective participant and study staff have addressed any questions or concerns, study staff will confirm the participant's willingness to participate and ask the participant to sign and date the consent documents. The participant may scan or take a photo of the signed signature page(s) and e-mail them back to the study staff using Azure RMS encrypted e-mail. Alternatively, during a videoconference call study staff can ask the participant to hold up the document so they can take a screen capture of the signature page using a VA-approved web-camera. Patient-participants may also opt to return their signed combined Informed Consent and HIPAA authorization forms and VA Form 10-5345, if applicable, via Azure RMS encrypted e-mail. For participants who have returned their combined Informed Consent and HIPAA Authorization form by mail, study staff will return a signed copy of the form to them via mail or Azure RMS encrypted e-mail.

Once study staff receive a participant's completed, signed and dated combined Informed Consent and HIPAA authorization form, they may call the participant and conduct the baseline telephone survey and schedule the biospecimen collection. Study staff may not access the participant's medical records, send genetic results to their provider, or collect any protected health information (PHI) or baseline data prior to receiving properly completed, signed and dated combined Informed Consent and HIPAA authorization forms from participants. Once study staff receive participants' combined Informed Consent and HIPAA authorization forms, they may scan or download the HIPAA authorization forms and store the scanned or downloaded pdfs in a secured folder behind the VA firewall. Hard copy versions of the combined Informed Consent and HIPAA authorization forms will be shredded after they are scanned and stored to the secured folder. All participants may opt to have their results sent to a non-VA healthcare provider. Participants who opt to have their results sent to a non-VA provider will be sent a Request for and Authorization to Release Health Information form, which will be included in the second recruitment mailing, alongside the cover letter, and combined Informed Consent and HIPAA authorization form.

iii. Baseline telephone visit:
After receiving the signed combined Informed Consent and HIPAA authorization form, study staff call the participant (see "GenoVA Telephone Scripts") to administer the baseline patient survey (see "GenoVA Baseline Survey") and schedule biospecimen collection.

iv. Genotyping:
Consented patient-participants undergo genome-wide genotyping, performed on either a mailed saliva sample or a blood sample obtained by phlebotomists at their local VABHS facility. By phone, study staff work with each participant to arrange for DNA specimen collection either by blood draw or by saliva sample. Participants may present to a VA Boston laboratory and undergo a blood draw of one EDTA tube (5 mL). If a participant already has an available EDTA blood sample in the laboratory (typically stored for 7 days after phlebotomy), that extant sample may be used instead. The VA Boston laboratory ships blood samples to an external VA-approved CLIA-certified laboratory for genotyping. Alternatively, the participant may choose to receive a coded saliva collection kit by mail, which he/she can ship to the laboratory using a pre-paid shipping package. Participants who opt to receive a coded saliva collection kit by mail will receive a package including the saliva collection kit, a user guide (see

"Oragene Saliva Kit User Guide"), instructions for sending their saliva specimen to the laboratory using a pre-paid shipping package (see "GenoVA Saliva Kit Packaging Instructions"), and a pre-paid shipping label.

The genotyping array includes millions of genetic markers, including those used to calculate the polygenic risk scores for the 6 target disease and a small number of markers associated with medically actionable findings for 59 conditions (described below in 5.6.v.) Patient-participants may choose either method for specimen collection (saliva or blood) depending on personal preference and/or convenience. Samples are coded using unique study IDs and do not include patient identifiers before shipment to an external VA-approved Clinical Laboratory Improvement Amendments (CLIA)-certified clinical laboratory, which performs the genotyping and calculates the polygenic risk scores. This laboratory generates a clinical polygenic risk report for each participant and sends it to the study staff.

v. Incidental actionable findings:
For patients undergoing clinical genome sequencing, the American College of Medical Genetics and Genomics (ACMG) currently recommends identifying and reporting incidental genetic findings for 59 conditions deemed medically actionable, primarily associated with cardiovascular disease and hereditary cancer syndromes (Kalia, *Genetics in Medicine* 2017). This number might increase over the course of the study. Although the GenoVA Study is not using genome sequencing, certain pathogenic and likely pathogenic variants in actionable ACMG genes are present on the genotype array the study is using. It is estimated that about 1-2% of individuals carry one of these variants. If the clinical laboratory identifies an actionable ACMG variant in a GenoVA Study participant's specimen, it confirms the finding with Sanger sequencing and reports any confirmed result back to the study staff. Adapting processes for return of incidental results developed for the Mass General Brigham Biobank, a GenoVA Study genetic counselor (GC) calls the participant to notify them that a genetic result that may be important to their health has been identified. The participant may choose to receive the result or decline (see "GenoVA Return of Incidental Results Phone Scripts"). If the participant declines to receive the result, the GC collects the reason for declining. The GC will review this information with the PI, who will use clinical judgment and consultation with the IRB to decide about any further action. If the participant agrees to receive the result, the GC conducts a standard genetic counseling session including: collection of family history, description of the disease associated with the actionable finding, discussion of potential implications for family members, facilitation of appropriate clinical follow-up (see "GenoVA Return of Incidental Results Phone Scripts"), and a letter relaying what was discussed during the genetic counseling session (see "GenoVA Patient Incidental Result Letter"). The participant also has the option of having the GC share the result with the participant's primary care provider (see "GenoA PCP Incidental Result Letter") and family members (see "GenoVA Family Incidental Result Letter"). Any participant with an actionable genetic variant will be withdrawn from the RCT portion of the study and will instead be followed along with the concurrent control group, although their data will not be analyzed together with the control group.

vi. Randomization:
Any participant with a confirmed actionable ACMG variant (estimated 1-2% of participants) is ineligible for subsequent stratified randomization and will instead be followed along with the concurrent control group. Among the remaining participants, those with at least one polygenic risk score (PRS) indicating and odds ratio (OR) >2.0 for any of the 6 target diseases are randomized to the PRS-high or usual care (UC)-high arm. Similarly, the stratum of patients with no PRS indicating high

genetic risk will be randomly allocated to having them and their PCP receive their results at baseline (PRS-average arm) or after 24 months (UC-average arm). Study staff use pre-generated randomization tables to assign participants to a study arm. Participants with an actionable ACMG variant are observed as concurrent controls. Study staff use pre-generated randomization tables to assign participants to a study arm.

vii. Delivery of intervention:
Patients assigned to the PRS-high and PRS-average arms receive a copy of their PRS report via the online patient portal and by letter (see "GenoVA Patient Average-Risk Results Letter (Immediate Results)" and "GenoVA Patient High-Risk Results Letter (Immediate Results)"). Their VABHS primary care providers also receive the report via CPRS and encrypted email (see "GenoVA PCP Average-Risk Results Letter" and "GenoVA PCP High-Risk Results Letter"). For participants with high genetic results (PRS-high arm), a clinician member of the study team (MD or genetic counselor) will contact them by phone (see "GenoVA High-Risk Results Phone Scripts") prior to sending the patient and his/her provider(s) the patient and provider reports, accompanied by evidence-based recommendations for screening, prevention, and diagnosis of the target conditions (see "Atrial Fibrillation Patient Information Sheet," "Breast Cancer Patient Information Sheet," "Colorectal Cancer Patient Information Sheet," "Coronary Artery Disease Patient Information Sheet," "Prostate Cancer Patient Information Sheet," "Type 2 Diabetes Patient Information Sheet," "Atrial Fibrillation Provider Information Sheet," "Breast Cancer Provider Information Sheet," "Colorectal Cancer Provider Information Sheet," "Coronary Artery Disease Provider Information Sheet," "Prostate Cancer Provider Information Sheet," and "Type 2 Diabetes Provider Information Sheet"). Patient-participants have the option to request that study staff send their PRS results and accompanying disease information sheet(s), and if applicable any non-VA providers patient-participants have authorized to release their information to, via Azure RMS encrypted e-mail. Genetic results reports are included in CPRS as a laboratory order that refers providers to a scanned pdf report in the patients' medical record (VistA). Patients assigned to the UC-high and UC-average arms receive the same intervention at the end of the study (after 24 months), after completion of the end-of-study survey. All participants with an actionable genetic variant will receive a copy of their PRS report prior to withdrawal from the RCT. All participants may opt to have their results sent to a non-VA healthcare provider.

Condition	Recommendations delivered to PCPs for high-risk patients
CAD	• Assess for symptoms such as angina or dyspnea and consider diagnostic testing, if present • Consider screening with stress testing or coronary computed tomography if patient is starting vigorous exercise program[97,98] • Optimize risk factors, such as blood pressure, smoking, lipids, and body-mass index[93,99]
AFib	• Assess for signs and symptoms such as irregular heart rhythm, palpitations, weakness, and dyspnea and consider diagnostic testing with office or ambulatory ECG monitoring, if present[100] • Optimize risk factors, including alcohol consumption[101]
T2D	• Assess for signs and symptoms, including polyuria, polydipsia, or neuropathy • Screen with hemoglobin A1c, fasting glucose, or 2-hour oral glucose tolerance test, if appropriate[102,103] • Optimize risk factors, including body-mass index and sedentariness[104,105]
Colorectal cancer	• Assess for symptoms including change in bowel habits or rectal bleeding, and evaluate as indicated • Screen with a high-sensitivity stool-based test or structural examination (e.g. colonoscopy) based on age, family history, and patient preferences[106,107] • Optimize risk factors, including smoking[108] and processed meat consumption[109]
Breast cancer (women only)	• Assess for signs and symptoms such as breast masses, overlying skin changes, or nipple discharge, and evaluate as indicated • Screen with mammography as appropriate, based on age, family history, patient preferences, and prediction models such as the Gail model and others[110-112] • Optimize risk factors, including smoking and alcohol consumption[113-115]
Prostate cancer (men only)	• Assess for signs and symptoms such as bone pain and prostate nodules or asymmetry and evaluate as appropriate • Screen with prostate-specific antigen testing as appropriate, based on age, family history, race, and patient preferences[116] • Optimize risk factors, including smoking[117]

Table 1: Evidence-based recommendations for screening and risk management for 6 target diseases

viii. End-of-study telephone visit:
24 months after enrollment, study staff administer a brief telephone survey to enrolled patient-participants (see "GenoVA End-of-Survey Telephone Script" and "GenoVA End-of-Study Survey"). The end-of-study telephone survey also asks patient-participants whether they had a new diagnosis of any of the six diseases during the study period. For any affirmative response, if applicable, the study staff may ask participants to request that their relevant medical records from outside healthcare providers be sent to study staff for review.

ix. End-of-study chart review:
Clinical chart reviewers blinded to patient-participant randomization status independently review each patient's medical record for the 24 months after enrollment for any evidence that one of the target diseases has been diagnosed since enrollment. VA databases including the Corporate Data Warehouse (CDW) and HERC Managerial Cost Accounting (MCA) are also accessed for other clinical and economic study outcomes. Centers for Medicaid and Medicare (CMS) data may also be requested, to identify study outcomes occurring outside of VA.

x. End-of-study results reporting
Participants randomized to the UC-high and UC-average arms and their providers receive the study intervention after completion of the end-of-study survey (see "GenoVA Patient Average-Risk Results

Letter (Delayed Results),""GenoVA Patient High-Risk Results Letter (Delayed Results)," "GenoVA PCP Average-Risk Results Letter," and "GenoVA PCP High-Risk Results Letter").

5.7. Does the study involve the use of deception and/or incomplete disclosure?
☒No ☐Yes:

5.8. When all research-related study procedures are complete, are there plans for long-term follow up?
☒No ☐Yes:

5.9. Does the study involve the collection of specimens (e.g. blood, cells, tissues, fluids, secretions, recombinant or synthetic nucleic acids, biological toxins, bacteria, virus, fungi, etc.)
☐No ☒Yes:

We will apply for COMS approval. This proposal will also be reviewed by the Safety Committee at the VA Boston Healthcare System.

5.10. Does the study involve the use of existing data, documents, records, and/or specimens for secondary analysis?
☐No ☒Yes

Existing medical record data from active patients in the VA Boston Healthcare System will be reviewed to screen for patient eligibility. These data will be obtained through the VA Corporate Data Warehouse (CDW) and electronic health records (both behind the VA firewall) only by IRB-approved study personnel with the appropriate permissions.

5.11. Are there provisions for medical and/or psychological support resources available to participants (e.g., in the event of incidental findings, research-related stress)?
☐No ☒Yes: *If yes, describe the provisions and their availability.*

If a participant experiences adverse effects or expresses emotional distress related to study participation, including the receipt of high-risk results/score (PRS) or actionable finding, and requires medical attention based on the judgement of the PI (a physician) and/or the patient's provider, they will be referred for clinical assessment as appropriate. All serious such cases, including those requiring a referral to a mental health professional or other therapeutic intervention, will be reported to both the HMS and VABHS IRBs as required. Additionally, though not provided as part of this study, participants' primary care providers may choose to refer their patients to genetic counseling services.

5.12. Describe the data and safety monitoring plan for the study. This plan should outline how study progress will be monitored throughout the lifecycle of the research to ensure the safety of subjects, as well as the integrity and confidentiality of data.

The PI will ultimately oversee the entire study for safety. Overall, the risks to participating patients and providers are considered minimal and are not dissimilar from the risks inherent to routine clinical care. Moreover, the proposed study will occur within one healthcare system and thus includes the oversight

of providers in the clinical management of patients enrolled in the study. Data will be collected observationally through the patient electronic health record (EHR), accessible only to research staff, and through participant surveys and interviews. As such, the PI, a physician by training, and the research staff will be responsible for the day-to-day monitoring of patient safety and data protection throughout the conduct of this proposed research. Monitoring of patient safety and data protection will occur in conjunction with the regular operations and conduct of the study and will be commensurate with the relative risks associated with the proposed research. In addition to the regular monitoring of patient safety and data protection, the research team will complete all continuing reviews, event reporting, audits, and/or other requirements per the provisions and timelines set forth by HMS IRB, VABHS R&D, and/or National Institutes of Health (NIH)/National Human Genome Research Institute (NHGRI) policies for research involving human subjects.

Any concerns regarding the ethical conduct of the study, the safety of participants, or a breach in the protection of study data made by provider or patient participants, the study staff, or others will be promptly reported to the study PI and escalated accordingly to the IRB and/or other relevant research oversight committees.

5.13. Are there any anticipated circumstances under which participants will be withdrawn from the research without their consent?
☒No ☐Yes

6. Recruitment Methods ☐ N/A.

6.1. Indicate how, when, where, and by whom participants will be recruited. Provide a list of materials used to recruit participants, e.g., emails, posters, and/or scripts here.

Study staff perform a regular query of the Corporate Data Warehouse (CDW) and patients' electronic health records (EHR) to generate patient eligibility tables. Study staff then mail letters to potentially eligible patients. These letters explain the purpose and procedures of the study and include all required elements of the informed consent process. After at least two weeks, study staff follow each letter with a telephone call to the potential participant. During this call, staff confirm eligibility, review the informed consent information in detail, answer any questions, and obtain informed consent to participate. Study staff will ask the participant to sign and date the informed consent form and return by mail in an included stamped envelope. Social media are not used in recruitment. This study does not recruit participants with impaired decision-making capacity.

The following documents will be used to recruit patient-participants into this study:

1. "GenoVA Recruitment Letter"
2. "GenoVA Opt-Out Postcard"
3. "GenoVA Cover Letter"
4. "GenoVA Informed Consent Form and HIPAA Authorization"
5. "GenoVA Telephone Scripts"

7. Consent Process

7.1. Describe how the research team will invite participants to take part in the research and obtain consent to participate. If the research team will not obtain informed consent, provide justification for requesting a waiver or alteration of consent (and/or parental permission).

Study staff will mail letters to potentially eligible patients. These letters will briefly explain the purpose and procedures of the study and include all required elements of the informed consent process. After at least ten days, study staff will follow each letter with a telephone call to the potential participant to confirm eligibility, review the study details, answer any questions, and obtain informed consent to participate. Study staff will ask the participant to sign and date the enclosed combined Informed Consent and HIPAA authorization form ("GenoVA Informed Consent Form and HIPAA Authorization") and return by mail in an included stamped envelope.

7.2. Describe how the research team will document the consent process (e.g., participant/researcher will both sign and date the consent document; participants will thumbprint the consent document). If the research team will not obtain signature and date, provide justification for requesting a waiver or alteration of documentation of consent (and/or parental permission).

Combined Informed Consent and HIPAA authorization forms will be provided to potentially eligible patients by mail and reviewed with study staff by phone. Agreeable patients will provide consent to participate in the study and will sign and date the combined Informed Consent and HIPAA authorization form "GenoVA Informed Consent Form and HIPAA Authorization" and return it to the study team by mail. The consenting patient will be enrolled into the study upon receipt of the signed and dated combined Informed Consent and HIPAA authorization form by study staff.

7.3. Will participants be offered a copy of the consent information?
☒ Yes ☐ No:

7.4. If consent will be obtained in a language other than English, identify the language(s) that consent information will be provided, who will be responsible for translation, and the provisions for communicating this information to participants. ☒ N/A

7.5. If the research involves deception and/or incomplete disclosure, describe the debriefing process. Explain when participants will be debriefed, who will debrief them, and how they will be debriefed. ☒ N/A

8. HIPAA Privacy Protections ☐ N/A.

8.1. Describe plans for obtaining authorization to access protected health information or provide the rationale for a waiver of authorization.

A waiver of HIPAA authorization to screen the VABHS patient database for study eligibility has been approved by the VABHS IRB as it would not be feasible to obtain individual authorization from the

population of 50,000 patients. Patients who enroll in the study will grant authorization to access their PHI as a part of the informed consent process.

9. Vulnerable Populations ☐ N/A.

9.1. Identify all vulnerable populations (e.g., children; pregnant women, human fetuses, neonates; prisoners; elderly; economically disadvantaged; employees or students of the investigator or sponsor; undocumented individuals; refugees; racial and/or ethnic minorities; illiterate or low-literacy; military personnel; terminally ill; cognitively impaired or mentally ill; persons with a stigmatizing disease or condition, e.g. AIDS/HIV, etc.) and describe safeguards to protect their rights and welfare.

This study may include VA employees. VA employees' decision to participate in this study will have no bearing on their VA benefits, employment status, or ratings. In the event of a direct supervisory relationship between a member of the research team and an employee, such a research participant will be consented by research staff other than the employee's direct supervisor. Moreover, supervisors of VA employees participating in this study will not have access to their employees' study related data.

10. Risks

Risks may be physical, psychological, social, legal, reputational, and/or financial.

10.1. Describe the reasonably foreseeable risks, discomforts, and/or inconveniences to participants and/or the group/community to which they may belong. Indicate the probability, magnitude, and duration of each risk.

Patient-participants are subject to the following risks:

a. The patient-participants' providers may order unnecessary screening tests in response to PRS results or the medically actionable findings identified in 1-2% of participants. However, in routine clinical care, there is already much variation in provider behavior around disease screening for the 6 target diseases, and any screening test ordered in response to high-risk PRS results likely falls into the range of what would be considered reasonable medical management with a favorable benefit/risk ratio (e.g. hemoglobin A1c testing or colonoscopy). It is unlikely that providers initiate new medication therapy in response to PRS without first confirming a new disease diagnosis. For the medically actionable findings, the study genetic counselor will provide information and consultation to the patient-participant and his/her healthcare providers for recommended clinical management. Thus, this study poses risks not dissimilar to those of current standard of care for the screening and management of these diseases.
b. Patient-participants who chose to submit a blood sample for genotyping may experience temporary bruising, lightheadedness, or infection from phlebotomy.
c. They may experience psychological distress upon learning they have a high genetic susceptibility for a certain disease, including an unanticipated medically actionable finding.
d. If a medically actionable finding is identified in a participant (estimated 1-2% of participants), then his/her first-degree family members each have a 50% chance of also carrying the finding. There is the risk that these family members will not want to learn this information or will

experience distress upon learning it. The genetic counselor will discuss these risks with the participant before he/she consents to learn about the medically actionable result.

e. Although federal law prevents health insurance companies from discriminating against patients on the basis of genetic information, some insurance companies may deny life, disability, and long-term care coverage on the basis of genetic information, such as unanticipated medically actionable findings or the PRS used in this study.
f. There is the risk of breach of data privacy.
g. For active-duty military participants, study-related information that is included in the VA medical record is subject to fewer protections, including access by DOD personnel.

10.2. Identify whether any of the information collected, if disclosed outside of the research, could reasonably place the participant at risk of criminal or civil liability or be damaging to the participant's financial standing, employability, insurability, or reputation.

Although federal law prevents health insurance companies from discriminating against patients on the basis of genetic information, some insurance companies may deny life, disability, and long-term care coverage on the basis of genetic information, such as unanticipated actionable results or the PRS used in this study.

10.3. Outline provisions in place to minimize each risk identified above.

a. The risk that patient-participant's PCPs order unnecessary or harmful screening tests in response to PRS results is minimized by the clinical judgment of their treating PCPs. In routine clinical care, there is already much variation in provider behavior around disease screening for the 6 target diseases, and any screening test ordered in response to high-risk PRS results will likely fall into the range of what would be considered reasonable medical management with a favorable benefit/risk ratio (e.g. hemoglobin A1c testing or colonoscopy). It is unlikely that providers will initiate new medication therapy in response to PRS without first confirming a new disease diagnosis. The misinterpretation and misuse of PRS results will be minimized through the reporting of clear, concise test interpretations, coupled to evidence-based screening and risk management recommendations consistent with accepted medical practice.
b. The risk to patient-participants of bruising, lightheadedness, or infection from phlebotomy will be minimized by the use of trained clinical phlebotomists, who will adhere to usual clinical protocols for blood draws.
c. The risk to patient-participants of psychological distress upon learning they have a high genetic risk for a certain disease is minimized by the informed consent process, during which participants who might find such information distressing may choose not to participate. For participants who do enroll in the study, the risk of such distress is minimized by the delivery of the results both to the patient-participants and their healthcare providers with whom they have established therapeutic relationships.
d. The risk that patient-participants may experience discomfort/embarrassment with questions about personal health information will be minimized by the use of study staff trained to administer surveys with sensitivity and to emphasize to participants that they may choose not to answer any questions that make them uncomfortable.

e. Risk of breach of confidentiality is minimized through the appropriate management and security of clinical data per VABHS and HIPAA protocols for use of research data. Data are securely transmitted using VA approved methods, including FIPS 140-2 validated encryption. This includes transmission of PHI and other patient-participant data, including PRS results, between VABHS and the external clinical laboratory, where clinical genotyping and interpretation are performed. Patient data files (source and analytic) are stored behind the VA firewall, on a drive created specifically to house the data for this research project.

   A copy of patient mailing data only will be downloaded outside of the drive specifically created to house data files in a VA secured, study-specific SharePoint site, and behind the VA firewall where strict permissions will be set to limit viewing to IRB-approved study personnel. This will be done to allow for the use of the Microsoft mail merge software so patient letters and address labels can be created and printed in batches, increasing patient enrollment numbers to meet the study's grant time table. Patient mailing data will be in the form of CSV files and may include identifying variables for both patients and providers. Variables for patients/providers may include: ID, full name, title, institution code/ID, gender, mailing address, and any associated flags (i.e. temporary address), patient-provider relationship information, or other similar variables that are required to be able to send mail or that are named in the IRB-approved patient letter template. The use of the mail merge system can be completed within the secure SharePoint environment.

   Patient protected health information (PHI) are delinked from the final analytic dataset. All data are retained within the VA except in 2 instances. First, coded biospecimens with DNA are sent to an external VA-approved laboratory for genotyping. Although these specimens will have DNA, they will not be labeled with any patient identifiers. Biospecimens will be shipped by commercial shippers using chain of custody, minimizing the risk of data breach. Second, deidentified data (including genetic risk scores but not the full genetic array data) will be submitted to the dbGaP data repository, per NIH regulations.

   Only study personnel credentialed and approved by the IRB have access to study data stored in either physical or electronic environments. Once study team members are no longer a part of the research team, their access to data and research materials is terminated. We do not allow any unauthorized access to our servers or our datasets. No PHI is released to the public, nor is it published in any medical journal. Suspected information security and privacy incidents are reported within one hour to the Information Security and Privacy Officers. Data are kept indefinitely or until the law allows their destruction in accordance with the VA Record Control Schedule. Electronic records are destroyed, when allowed, in a manner in which they cannot be retrieved. Mobile devices will not be used in this study and thus will not contain the only copy of research information.

f. Active-duty military participants will be made aware of the potential for access of study-related data entered into the VA medical record by additional parties (DOD personnel) through the informed consent process. Prior to study participation, these participants will provide written consent to take part in study activities.

11. Benefits

11.1. Describe the potential benefits to individual participants, if any, and/or society. If there are no direct benefits, state that here. Note: payment/compensation is not a benefit.

The benefits to patients participating in this study include the potential for them to engage with their providers in therapeutic conversations about the risks and benefits of screening for and reducing the risk of 6 common diseases. Receipt of high-risk PRS or incidental actionable results might prompt providers to order appropriate screening tests they might have otherwise overlooked. Patients might be more adherent to recommended screening and risk-reducing behaviors if they feel the recommendations are personalized to them. Society will also benefit from the knowledge to be learned about the impact of introducing PRS testing into clinical care. These potential benefits outweigh the minimal potential risks to participants.

12. Participant Privacy

12.1. Describe provisions to protect participants' privacy (their ability to control and limit the extent, timing, and circumstances of sharing information about themselves with others, e.g., the use of a private interview room) and to minimize any sense of intrusiveness that may be caused by study questions or procedures.

Participants may schedule study telephone calls (baseline and end-of-study) with study staff at a time that is convenient for them. Similarly, they may present to the VA laboratory for phlebotomy at their convenience. During baseline and end-of-study surveys, participants may choose not to respond to some questions.

13. Data Confidentiality

13.1. Indicate the identifiability of the data/specimens:

☐ **Data/specimens will not contain any direct or indirect identifiers (anonymous data).**
☐ **Data/specimens will contain direct or indirect identifiers, but the research team will remove them upon receipt (de-identified data).**
☒ **Data/specimens will contain indirect identifiers (i.e., number, letter, symbol, or combination thereof) and the research team will maintain a key that links identifiers to individual participants (coded data).**
☐ **Data/specimens will contain direct identifiers (identifiable data).**
☐ **None of the above; describe:**

13.2. Have any identifiable data/specimens been de-identified for use in this research study?

☐ **No** ☒ **Yes:**

13.3. Identify where data/specimens will be stored (e.g., on campus at Harvard or remotely, in a specimen laboratory) and describe the provisions to maintain confidentiality (e.g., password protection, encryption, locked filing cabinets, etc.). Refer to the Investigator Manual and the Harvard Research Data Security Policy for additional information.

Procedures for the appropriate management and security of research data will be implemented per VABHS and HIPAA protocols for use of research data. Patient protected health information (PHI) will be delinked from the final analytic dataset. All data will be retained within the VA. Patient and provider data files (source and analytic) will be stored behind the VA firewall, on a drive created specifically to house the data for this research project. Only study personnel credentialed and approved by the IRB will have access to study data stored in either physical or electronic environments. Once

study team members are no longer a part of the research team, their access to data and research materials will be terminated. We will not allow any unauthorized access to our servers or our datasets. No PHI will be released to the public, nor will they be published in any medical journal. Suspected information security and privacy incidents will be reported within one hour to the Information Security and Privacy Officers. Data will be kept indefinitely or until the law allows their destruction in accordance with the VA Record Control Schedule. Electronic records will be destroyed, when allowed, in a manner in which they cannot be retrieved. The NIH will issue this study a Certificate of Confidentiality.

13.4. Describe whether any data/specimens will be transmitted and, if so, how, when, and to whom.

Biospecimens collected from patient-participants for genotyping will be collected at VA clinical laboratories and shipped to the Laboratory for Molecular Medicine per clinical channels for send-out laboratory tests, including chain of custody.

Data will be securely transmitted using VA approved methods, including FIPS 140-2 validated encryption. This will include transmission of PHI and other patient-participant data, including PRS results, between VABHS and the Laboratory for Molecular Medicine, where clinical genotyping and interpretation will be performed.

13.5. Indicate who is responsible for data/specimen management and how the research team and/or other collaborators are permitted access to information.

Only study personnel credentialed and approved by the VABHS IRB will have access to study data stored in either physical or electronic environments. Once study team members are no longer a part of the research team, their access to data and research materials will be terminated.

13.6. Indicate how long data/specimens will be stored and describe the plans at the end of the storage period (e.g., are data/specimens destroyed, returned to data/specimen provider, etc.).

Data will be kept indefinitely or until the law allows their destruction in accordance with the VA Record Control Schedule. Electronic records will be destroyed, when allowed, in a manner in which they cannot be retrieved. Biospecimens will be discarded by the Laboratory of Molecular Medicine after analysis and quality assurance are complete.

14. Data/Statistical Analyses Plan

14.1. Describe plans for analysis (including the statistical method, if applicable).

Intention-to-treat analyses compare the PRS-high and UC-high arms. The primary endpoint for efficacy is the time to a new diagnosis of one of 6 common complex diseases among patients with at least one PRS indicating high genetic risk. The analysis is based on the rate of new diagnosis at month 24 after randomization for the PRS-high and UC-high arms. We use the Cox model to analyze the data with the time to diagnosis. Further analyses examine time-to-new diagnosis for specific diseases separately. Moreover, analyses where summary PRS scores are included in statistical models, as well

as demographic factors such as age, gender, socioeconomic status, and baseline health as covariates, are conducted. Additional analyses make outcomes comparisons between the randomized PRS-average and UC-average arms. Differences between the UC-high group and the UC-average group quantify the disease risk elevation among patients with $OR_{PRS}>2.0$ compared to those with all $OR_{PRS}<2.0$. Differences between the UC-high and PRS-high arms will quantify the impact of telling high-risk patients and their PCPs about their high risk. Data from the 1-2% of participants excluded from the RCT because of a medically actionable finding will be analyzed separately in exploratory analyses.

14.2. Is there a sample size/power calculation?
☐ **No** ☒ **Yes:**

A total of 1,076 patient-participants are genotyped. Based on published estimates of the prevalence of high-risk PRS values, we make the conservative assumption that 33% of genotyped patient-participants have at least one $OR_{PRS}>2.0$ across all diseases.

In review of data VABHS from 2014-2017 (Table 2), based on published algorithms using ICD and CPT codes, among patients 50-70 years old, an average 6.2% had a new target diagnosis per year. If we assume that 12% of patients in the control arm will have a new target diagnosis over the 2-year study period and that delivery of PRS results and recommendations will increase this to 24% of patients in the intervention arm during the same period (RR=2), a total sample size of 320 patient-participants must be included in the RCT to detect this difference at a two-tailed $\alpha=0.05$ and $\beta=0.20$ (power of 80%). It is likely that patients with higher genetic risk ($OR_{PRS}>2.0$) have a higher disease incidence than that observed in the general VABHS population. If the incidence in the $OR_{PRS}>2.0$ group is 15%, then 320 patient-participants give us the same power to detect an increase to 28% in the PRS arm (RR 1.87). If 33% of genotyped patient-participants have at least one $OR_{PRS}>2.0$ and are enrolled in the RCT, a total sample size of 960 genotyped patient-participants is needed. To account for potential clustering effect among patients receiving care from the same providers, we include a design effect of 1.10, based on an estimate of 7 enrollees per PCP and an intraclass correlation coefficient of 0.02 (Glynn, Medical Care, 2007). As a result, a total of 960 x 1.1 = 1,056 participants would be needed. We will enroll a total of 1,076 to account for the 1-2% of participants who will be excluded from randomization due to an actionable ACMG variant.

	2014	2015	2016	2017	Average
Total eligible patients	6,145	6,083	6,016	5,770	6,003
Total patients diagnosed	372(6.1%)	340(5.6%)	388(6.4%)	400(6.9%)	375(6.2%)
By disease					
CAD	113(1.8%)	106(1.7%)	126(2.1%)	130(2.3%)	119(2.0%)
Atrial	51(0.8%)	60(1.0%)	71(1.2%)	62(1.1%)	61(1.0%)
fibrillation T20	156(2.5%)	113(1.9%)	127(2.1%)	156(2.7%)	138(2.3%)
Colorectal cancer	8(0.1%)	10(0.2%)	13(0.2%)	11(0.2%)	11(0.2%)
Breast cancer	1(0.0%)	1(0.0%)	3(0.0%)	5(0.0%)	2(0.0%)
Prostate cancer	43(0.7%)	50(0.8%)	48(0.8%)	36(0.6%)	44(0.7%)

Table 2. Annual rates of new diagnoses for six target diseases in patients between the ages of 50-70 years old across VA Boston Healthcare System, 2014-2017, by disease

Diagnosis estimates based on age or first diagnosis or at least one or the six target diseases. Annual estimates based on primary care relationship over two-year period with no new diagnosis or a target disease during first year.

15. Costs and Compensation ☐ **N/A.**

15.1. Identify any costs that participants may incur during the study, including transportation costs, childcare, or other out-of-pocket expenses.

Patient-participants will incur the costs of time and travel for a one-time blood draw or saliva sample collection at a VA lab.

15.2. Identify remuneration that participants may receive during the study. Specify the amount, timing of disbursement, and method (e.g. money, gift cards, in-kind, incentives, raffles, and transportation). Describe how compensation will be calculated and paid if a participant withdraws. If any participant will receive a single payment more than $100, or $600 or more in one calendar year, refer to Harvard University Financial Policy on Human Subject Payments.

Each patient-participant will receive cash or a gift card worth $30 upon completion of the baseline survey and biospecimen collection and another $30 of cash or gift card after completion of the end-of-study survey (24 months after enrollment).

16. Sharing Study Results ☐ **N/A.** *Skip to next section.*

16.1. Describe the plan to share study results with individual participants, the participant group/community, and/or others.

Information associated with this proposed clinical trial will be disseminated according to the National Institutes of Health (NIH) Policy on the Dissemination of NIH-Funded Clinical Trials by the research team as follows:

• This proposed trial, including all required details, will be registered with ClinicalTrials.gov.
• Informed consent documents for this proposed trial will contain language informing any and all potential participants of our intent to post a description of the study and a summary of its results to ClinicalTrials.gov.
• Information and updates associated with this proposed trial will be reported to ClinicalTrials.gov per the NIH Policy's required provisions and timeframes, including adherence to the timelines for trial registration and submission of results.

Furthermore, in order to more broadly disseminate information about the proposed trial to potential stakeholders, including policymakers, researchers, health care providers, and patient communities, we plan to:

• Present information regarding the purpose, methods, and results of the proposed trial at local and informal meetings throughout the HMS and VABHS systems.
• Analyze trial data and present findings at the annual meetings of the American College of Medical Genetics and Genomics (ACMG), American Society of Human Genetics (ASHG), Society of General Internal Medicine (SGIM), and other pertinent academic venues.
• Submit trial results for peer review and publication in academic and medical journals.

17. Research Related Injuries ☐ **N/A.** *Skip to next section.*

17.1. Describe plans for medical care and compensation for research-related injuries.

Phlebotomy-related injuries will be managed by clinical protocols already in place by the clinical phlebotomists who will be performing the blood draw.

18. Reportable Events

18.1. Outline plans for communicating reportable events to the IRB, Sponsor, or others as applicable (e.g., adverse events, unanticipated problems involving risks to participants or others, breach of confidentiality).

We anticipate very few, if any, adverse effects (AE) during the course of the study, but we nonetheless have a process in place to identify and address AE if they occur. An AE will be defined as any unanticipated or unintended medical occurrence, which does not necessarily have a causal relationship with the study condition, procedure(s) or study agent(s), that occurs after the informed consent is obtained. Preexisting conditions or illnesses which are expected to exacerbate or worsen are not considered adverse events and will be accounted for in the subject's medical history. A serious adverse event (SAE) will be defined as an AE resulting in one of the following outcomes: death during the 24 months after enrollment, life threatening event (defined as an event that places a participant at immediate risk of death), inpatient hospitalization, and any other condition which, in the judgment of the investigator, represents a significant hazard, such as an important medical event that does not result in one of the above outcomes. An event may be considered an SAE when it jeopardizes the participant or requires medical or surgical intervention to prevent one of the outcomes listed above. AEs may be observed by the study staff or volunteered by VABHS providers and patients. All AEs or SAEs will be assessed for relationship to the study research procedures, to determine whether study participation was likely to have caused the AE/SAE. AEs related to study participation that are reported to research personnel will be recorded on an AE form in an electronic database.

The Principal Investigator at VABHS reports unanticipated problems, deaths, study-related AEs, and safety monitors' reports to the IRB in accordance with VHA Handbook 1058.01 and VABHS IRB SOP. These events will also be reported to the Harvard Medical School IRB in accordance with federal and local policies, without using participant identifiers.

Suspected information security and privacy incidents will be reported within one hour to the Information Security and Privacy Officers at VABHS.

19. Regulatory Compliance

19.1. Describe plans for monitoring regulatory compliance. The monitoring plan should include how you will ensure proper record keeping, retention of required regulatory documents and participant files, and adherence to the IRB-approved protocol and/or IRB policies and procedures. Monitoring plans should describe 1) who is responsible for file maintenance, 2) what will be maintained, 3) how often files will be reviewed and using what method, and 4) where documentation will be retained (for both Regulatory Documents and Participant files).

The project manager will be responsible for file maintenance, including all communications with the IRB and other regulatory bodies. Files including enrollment logs and documentation of informed consent will be audited at least annually by the VABHS Research Compliance Office.

20. Data or Specimen Banking (Repositories) ☐ N/A.

20.1. Identify what data/specimens will be collected for the repository and what information will be associated with the data/specimens.

Study data will be stored in two data repositories, as described below. Genomic data stored in each repository will include individual-level, array derived genotypes from the SNP arrays used in this study. This study will not perform whole genome or whole exome sequencing but may identify actionable incidental findings beyond the 6 targeted diseases of the study (specifically, actionable ACMG variants). Both data repositories comply with Veterans Health Administration (VHA) Handbook 1200.12 and local VABHS IRB Standard Operating Procedures (SOP). The study PI will be responsible for ensuring the submission of study data to dbGaP and the GenoVA Data Repository.

NCBI Database of Genotypes and Phenotypes (dbGaP)

Deidentified study data from the patient-enrollees in this study are submitted to the NCBI dbGaP. This includes the SNP array data and the presence/absence of diagnosis of the 6 target diseases in the study. External researchers may request access to these data through a Data Use Certification (DUC) Agreement on the dbGaP website.

GenoVA Data Repository

A separate data repository is stored behind the VA firewall that includes de-identified individual-level trial data, including SNP array data, demographics, diagnoses, and survey data. Researchers outside VHA with an IRB-approved protocol may request access to these data.

20.2. Describe where and how long the data/specimens will be stored, who will have/may request access, and how data/specimens will be accessed.

Data on dbGaP will be available to any authorized investigator via a data access request (controlled access). Researchers outside VA with an IRB-approved protocol may request access to de-identified trial-level data stored within the GenoVA Data Repository.

20.3. Indicate whether participants' permission will be obtained to use the data/specimens in other future research projects.

No, participants will be informed upon enrollment into the study that their de-identified data may be used for future research by authorized researchers.

20.4. Describe the procedures to release data/specimens.

Data will be requested through dbGaP via a data access request. If the request is approved, data will be released for use only as consistent with an effected data use agreement. Researchers interested in

accessing the GenoVA Data Repository may request access with an IRB-approved protocol via local VABHS data request and access mechanisms.

20.5. Describe the plan to send data/specimens to research collaborators outside of Harvard.
☐ **N/A**

We will use secure file transfer protocol (SFTP) to upload study metadata in the form of a data dictionary and relevant phenotype data resulting from this research to dbGaP. The GenoVA Data Repository will be stored behind the VA firewall and will be accessible only to VA-approved researchers.

20.6. Describe the plan to receive data/specimens from collaborators outside of Harvard.
☒ **N/A**

21. Clinical Trials ☐ **N/A.** *Skip to next section.*
Complete this section for NIH funded clinical trials or applicable clinical trials (ACT) under the FDA Amendments Act.

21.1. Describe plans for registering this project in a clinical trials registry, e.g., clinicaltrials.gov. If available, provide the registry record number.

This trial has been registered at clinicaltrials.gov. The trial's registry record number is NCT04331535.

22. Device *This section should be completed if the study involves the use of any device on/in/with human subjects.* ☒ **N/A.** *Skip this section.*

22.1. Describe the device, including the generic or common name, brand name (if applicable), purpose, function/operation, and whether it is an implant. Indicate who is providing this device for research use.

22.2. Indicate the FDA status of the device as it is being used for the proposed research:
☐ FDA-approved device being used "on-label" (i.e., FDA-approved purpose, population, manner).
☐ FDA-approved device that is being used "off-label" (i.e., for a different purpose, population, or in a different manner than approved).
☐ Not approved by the FDA.

22.3. Indicate the IDE Status of this device:
☐ The use of this device has an IDE.
☐ The use of the device qualifies for an Abbreviated IDE.
☐ The use of the device is exempt from the IDE requirements.

22.4. Has the FDA made a determination as to whether the device is Significant Risk or Non-Significant Risk? ☐ **No** ☐ **Yes:** *If yes, indicate the FDA's determination.*

22.5. Describe plans for storage control, and dispending of the product so that (1) only authorized investigators will use the product; (2) the product will only be used in participants who have provided consent, and (3) there will be documented tracking of each product, including unique identifiers and any return/disposal.

23. Drug/Biologic *This section should be completed if the study involves the use of any drug/biologic on/in/with human subjects.* ☒ **N/A.** *Skip this section.*

23.1. Describe the drug or biologic, including the generic or common name, brand name (if applicable), dosing, route of administration, number of doses, timing of administration. Indicate who is providing the drug, biologic, supplement for research use.

23.2. Indicate the IND Status of this drug or biologic and who holds the IND:

☐ There is an IND approval from the FDA for the use of this item.
The IND is held by:

☐ An IND application has been, or will be, submitted to the FDA.
The IND will be held by:

☐ An IND approval is not required.

23.3. Describe how dispensing, delivery and administration will be performed, and by whom. Include information about control (e.g., locked storage), tracking (e.g., lot number, returned pills), documentation, storage, and return/disposal.

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