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ARTICLE

Returning actionable genomic results in a research biobank: Analytic validity, clinical implementation, and resource utilization

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Summary

Over 100 million research participants around the world have had research array-based genotyping (GT) or genome sequencing (GS), but only a small fraction of these have been offered return of actionable genomic findings (gRoR). Between 2017 and 2021, we analyzed genomic results from 36,417 participants in the Mass General Brigham Biobank and offered to confirm and return pathogenic and likely pathogenic variants (PLPVs) in 59 genes. Variant verification prior to participant recontact revealed that GT falsely identified PLPVs in 44.9% of samples, and GT failed to identify 72.0% of PLPVs detected in a subset of samples that were also sequenced. GT and GS detected verified PLPVs in 1% and 2.5% of the cohort, respectively. Of 256 participants who were alerted that they carried actionable PLPVs, 37.5% actively or passively declined further disclosure. 76.3% of those carrying PLPVs were unaware that they were carrying the variant, and over half of those met published professional criteria for genetic testing but had never been tested. This gRoR protocol cost approximately $129,000 USD per year in laboratory testing and research staff support, representing $14 per participant whose DNA was analyzed or $3,224 per participant in whom a PLPV was confirmed and disclosed. These data provide logistical details around gRoR that could help other investigators planning to return genomic results.

Introduction

Research biobanks and other human research studies that collect and analyze DNA are increasingly confronted with the question of whether and how to return actionable genomic results to individual participants (gRoR). A majority of research participants[1–3] and researchers[4,5] favor returning such results to participants, and many research studies that collect genomic data have written policies encouraging the return of actionable genomic results to participants (gRoR).[6–9] Yet the vast majority of such studies in the US and around the world have not implemented gRoR because of uncertainties around how to consent participants; which genes to select for return; how to analyze, classify, and report research variants; the logistics of recontacting participants; regulatory requirements necessitating the confirmation of research results; the transition of research participants into an appropriate clinical workstream; and the effort and cost associated with each of these steps.[10–17] Despite these challenges, it is likely that research participants will increasingly expect gRoR in genomic research.[18,19] For example, the NIH-sponsored All of Us research program has announced that it will sequence and return actionable genomic results to 1 million Americans,[20] adopting a process similar to that described in this article, and a 2018 National Academies of Science, Engineering, and Medicine report predicted "the return of research results will soon become an integral part of the research enterprise" and stressed the need for detailed descriptions of consent practices, technical standards, participant preferences, and resourcing for returning research results.[21]

Research studies and biobanks that have elected to return genomic information to research participants typically share common themes and workflows.[22–25] First, participants must explicitly accept or decline gRoR at enrollment, or if this choice was not presented at enrollment, they must later be re-consented for gRoR. Next, a list of genes associated with actionable hereditary conditions is selected for analysis and potential return. Then, genotyping (GT) or genome sequencing (GS) data are filtered and interpreted by a clinical genetics laboratory

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in order to identify variants eligible for return. Participants are re-contacted without disclosing the specific research result, and a second sample is requested that can be confirmed with clinical testing. Upon confirmation, the result is communicated, most often by a genetic counselor or physician associated with the study, who then assists the participant in pursuing appropriate referrals. The complexity and costs of implementing this gRoR template are intimidating to most researchers, and detailed logistical data, time utilization, and costs from sites conducting gRoR have not been previously reported. In this report, we provide a comprehensive overview of one gRoR protocol within the biobank of a large healthcare system and present detailed data on consent processes, initial research laboratory analysis and verification, recontact efforts, clinical laboratory confirmation of research findings, results disclosure, and clinical referral among biobank participants, as well as the effort and costs required to carry out such a protocol.

Material and methods

Protocol design

The Mass General Brigham Biobank (MBG Biobank) is a research biorepository in an academic medical center linked to electronic health records (EHRs).[26] The protocol was approved by the Mass General Brigham Institutional Review Board (IRB). An MGB Biobank Return of Results Committee designed the protocol for recontact and disclosure of genomic results with input from participant stakeholders and the IRB. The consent and disclosure process followed an incremental disclosure protocol in which participants were consented upon biobank enrollment with the explicit understanding that their DNA would be analyzed for research and that they might be recontacted if "medically important" results were discovered (Note S1). The option to decline recontact was not available if participants consented to enroll in the biobank.

The genes selected for gRoR were the 59 genes in the 2nd version of the American College of Medical Genetics and Genomics (ACMG v.2) recommended list to be evaluated for return of secondary findings during indication-based sequencing.[27,28] In these genes, only pathogenic or likely pathogenic variants (PLPVs) classified according to the ACMG and American College of Molecular Pathologists (AMP) criteria met our reporting criteria for return (Figure 1).[29]

For those participants in whom a PLPV was discovered in an ACMG v.2 gene (Table 1), a disclosure team of one part-time study-supported genetic counselor (sGC) and two part-time study-supported medical geneticists (sMGs) organized and implemented the workflow, notified participants, collected samples for Clinical Laboratory Improvement Amendments (CLIA) confirmation, and facilitated final disclosure and clinical follow-up (Figure 2). Participants who had verified PLPVs in one of the genes on the ACMG v.2 gene list, who were still living, and who did not have prior personal knowledge or EHR record of the variant were considered eligible.

Eligible participants were sent a letter alerting them to an actionable DNA finding without specifics, followed by a sGC call, with letters and calls repeated for up to seven total contact attempts (Note S2, Note S3, Table S1). If the participant was never reached but had a known address, a final certified letter was sent. Additional phone calls were made as needed and in response to participant requests and returning missed calls, and contact attempts were logged in a REDcap database (Figure 3, Figure S1). In January 2021, the number of letters sent was reduced from four to two letters, a first letter and a final certified letter. After reaching a participant, the sGC followed a phone script (Note S3) reminding them of their participation in the biobank, reiterating that a DNA result of medical importance had been identified, and asking if they wished to hear more. If they agreed to hear more, the sGC described the specific condition associated with the genetic finding (e.g., colon cancer), but did not specify the gene or variant (Table S1), and counseled the participant about the implications of gRoR while collecting a brief medical and family history. Participants were given the opportunity to continue, or opt out, of a CLIA-approved laboratory confirmation (CLC) and results disclosure (Figures 2 and 3, Figure S1). For participants who wished to continue, a clinical saliva or blood sample was collected and accessioned by the CLIA-approved MGB Laboratory for Molecular Medicine (LMM), and variants were confirmed by Sanger sequencing in a CLIA-compliant workflow. Laboratory results were finalized into a clinical report (Note S4) and shared with the sGC who assisted in identifying a provider (a medical geneticist, disease specialist, or their own PCP if requested) to handle disclosure in a conventional clinical appointment to ensure appropriate medical follow-up. MGB specialists or the sMGs returned results if the participant's provider was unwilling to do so. The cost of CLC genetic testing was covered by the study, but the disclosure visit was considered a clinical service to be covered by a participant's own medical insurance and was scheduled with a physician who was prepared to contextualize the CLC finding, document the result in the official medical record, and make further referrals and follow-up as medically indicated (Figure 2). The responsibility of the research team was considered to have ended when the clinician disclosed the clinical report to the participant.

Laboratory methods

Genomic data

Details on the genomic datasets can be found in supplementary lab methods (Methods S1). In brief, we analyzed (1) genotyping data from 36,417 MGB Biobank samples utilizing one of three versions of the Illumina (San Diego, CA) Infinium Multi-Ethnic Genotyping array, (2) sequencing data from 2,349 individuals for a limited set of genes as part of the Electronic Medical Records and Genomics (eMERGE) III program,[30] and (3) exome sequencing data from 914 individuals who self-reported as Hispanic or Latino, Black or African American, or other in the MGB EHR.

Variant interpretation

Variants were filtered to a list of 59 genes included in ACMG v.2 (Table S2).[27,28] For comparisons in the paper, we divided the ACMG v.2 genes into the following categories: cancer (*SDHD*, *SDHAF2*, *SDHC*, *SDHB*, *STK11*, *PTEN*, *MEN1*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *APC*, *BRCA1*, *BRCA2*, *RET*, *BMPR1A*, *SMAD4*, *TP53*, *RB1*, *VHL*, and *WT1*); cardiac disease (*MYH7*, *TPM1*, *PRKAG2*, *TNNI3*, *MYL3*, *MYL2*, *ACTC1*, *TMEM43*, *DSP*, *PKP2*, *DSG2*, *DSC2*, *SCN5A*, *RYR2*, *LMNA*, *MYBPC3*, *GLA*, *TNNT2*, *KCNQ1*, *KCNH2*, *COL3A1*, *MYH11*, *ACTA2*, *TGFBR1*, *TGFBR2*, *SMAD3*, and *FBN1*); familial hypercholesterolemia (*APOB*, *LDLR*, and *PCSK9*); and other actionable diseases (*ATP7B*, *RYR1*, *CACNA1S*, *OTC*, *TSC1*, *NF2*, and *TSC2*). The variant calls within the set of 59 genes were annotated via multiple data sources, including Alamut (Alamut Batch, SOPHiA GENETICS, Lausanne, Switzerland), the Genome Aggregation Database (gnomAD),[31]

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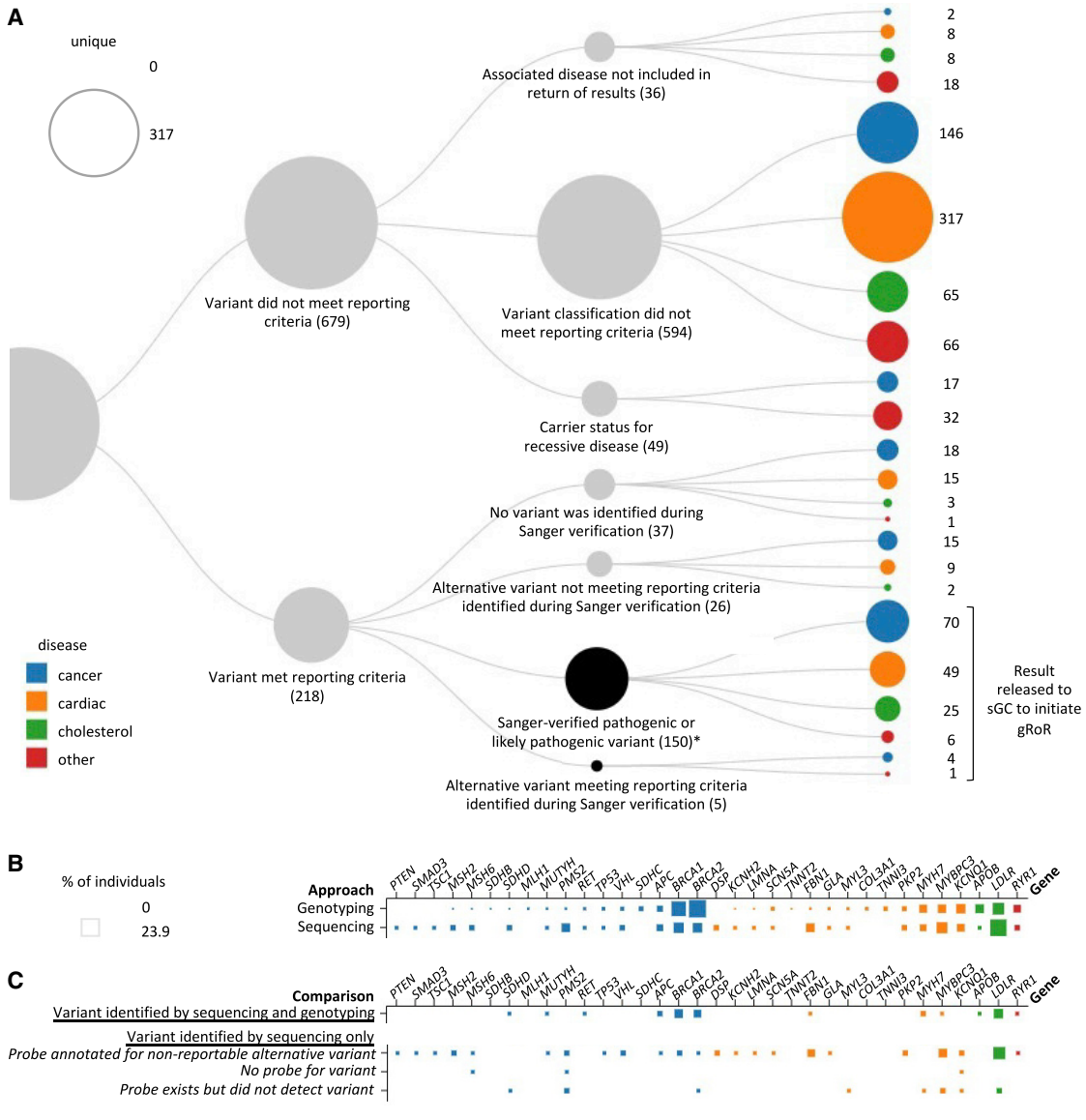

Figure 1. Interpretation of research data and yield per platform, disease area, and gene

(A) Flowchart of research interpretation of unique variants revealed in genotype (GT) data. Among 36,417 participants whose DNA was analyzed by GT, 218 unique variants initially met criteria for return, out of which, 155 were replicated or revealed to have alternative reportable variants through Sanger verification of a second (non-CLIA) research sample. Asterisk indicates that this includes three variants that were downgraded after initiation of the gRoR process. Colors correspond to disease areas: cancer (blue), cardiac (orange), cholesterol metabolism (green), and other actionable conditions (red).

(B) Among the 36,417 participants whose DNA was analyzed by GT and the 3,263 participants whose DNA was analyzed by genome sequencing (GS), the percentage of cases per gene is represented by the size of the squares, showing the differences in relative frequency of genes by each platform, using the same color coding as above.

(C) Among the 3,263 participants who were additionally analyzed by GS, squares represent the percentage of variants in each gene that were either also identified by GT or identified by sequencing only, along with the reasons that the variant was missed by GT for each gene.

ClinVar,[32] the Human Genome Mutation Database (HGMD),[33] and the GeneInsight Suite (Sunquest, Tucson, AZ).[34] The annotated variants were filtered with the GeneInsight Suite to find (1) variants previously identified as disease causing by the MGB LMM, (2) variants classified as P/LP within ClinVar with a minor allele frequency (MAF) < 5.0%, (3) variants classified as a disease-causing mutation (DM) in HGMD with an MAF < 5.0%, and (4) loss-of-function variants (nonsense, frameshift, canonical splice-site, and initiating methionine variants) with an MAF < 1.0% (Table S2, Table S3). Variants of uncertain significance (VUSs) were not reported, however some variants were downgraded to VUSs over the course of the study (Figure 2, Table 2, Table S4). Clinical variant classification was carried out in accordance with the criteria set by the guidelines by the ACMG and AMP,[29] with disease-specific modifications as recommended by the Clinical Genome Resource Expert Panels.[35] We conducted verification of PLPVs on the research sample prior to initiation of gRoR to

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Table 1. Demographics of biobank participants

Characteristic	Biobank participants N = 124,391	DNA was analyzed N = 36,417	Returnable finding identified N = 425	Eligible for return N = 293	Result disclosed or disclosure in progress N = 153
Female sex—no. (%)	70,612 (56.8%)	19,713 (54.1%)	232 (54.6%)	149 (50.9%)	79 (51.6%)
Age—years	56.1 (±17.7)	59.9 (±17.1)	59.3 (±16.2)	59.0 (±16.7)	58.2 (±15.6)
Race/ethnicity—no. (%)					
Non-Hispanic white	103,587 (83.3%)	30,302 (83.2%)	361 (84.9%)	245 (83.6%)	134 (87.6%)
Non-Hispanic Black	5,652 (4.5%)	1,758 (4.8%)	19 (4.5%)	14 (4.8%)	4 (2.6%)
Non-Hispanic Asian	3,662 (2.9%)	815 (2.2%)	7 (1.6%)	6 (2.0%)	3 (2.0%)
Hispanic	6,394 (5.1%)	2,227 (6.1%)	27 (6.4%)	19 (6.5%)	7 (4.6%)
Unknown/other	5,095 (4.1%)	1,315 (3.6%)	12 (2.8%)	9 (3.1%)	5 (3.3%)

Plus-minus values are means ± SD. Percentages may not total 100 because of rounding.

ensure accuracy; for genotyping results, research verifications were not conducted once the variant call was determined to be high confidence or a clear false positive. Only PLPVs associated with disorders listed in the ACMG v.2 gene list[28] were returned to participant and if seen with the following genotypes: heterozygous, homozygous, or bi-allelic PLPVs for autosomal-dominant conditions; homozygous or bi-allelic PLPVs for autosomal-recessive conditions; and heterozygous, homozygous, hemizygous, or bi-allelic PLPVs for X-linked conditions (Figure 1).

Electronic health record review

In participants who were identified to have a returnable variant, we reviewed the EHR for medical and family history and assessed whether, prior to disclosure, participants met published criteria from the National Comprehensive Cancer Network (NCCN) for genetic testing for colorectal and hereditary breast and ovarian cancer predisposition,[36–38] or professional society/expert guidelines for other genes leading to cancer predisposition, where NCCN guidelines were not available (see Else et al. GeneReviews and van Leeuwaarde et al. GeneReviews in web resources), as well as modified Dutch Lipid Clinic Network (DLCN) criteria for familial hypercholesterolemia (FH) (not awarding points for discovery of the genetic variant).[39,40] We then assessed whether obtaining additional targeted personal and family history at the time of notification and disclosure would have changed that participant's eligibility for recommended clinical genetic testing (Figure 4).

Surveys

We sent participants who opted in for gRoR surveys by email, or if requested by mail, at baseline (after notification but before clinical disclosure), 1 month after genomic results disclosure, and 6 months after disclosure to assess their decisional regret with gRoR by using a published 5-item decision regret scale.[41] Responses at 1 and 6 months after disclosure were converted to a 0–100 score based on scale instructions; higher scores indicated greater regret about that decision. Scores above 50 were considered to indicate overall regret (i.e., a tendency to agree with statements such as "I regret the choice that was made").

Interviews

Among the 65 active and 31 passive decliners, a convenience sample of 51 (34 active and 17 passive) decliners were contacted to ascertain reasons for declining (Note S5). Twenty-four (17 active and 7 passive) decliners verbally consented to semi-structured phone interviews. Interviews, lasting 5–25 min, were audio recorded, transcribed, and uploaded into NVivo 12 (QSR International, Melbourne, Australia). We used a codebook developed by two coders (M.U. and J.S.) to perform consensus coding on transcripts by using thematic analysis. Codes were grouped according to similar themes, representing reasons for declining.

Budget impact and cost analysis

We conducted a time and budget impact analysis to estimate the incremental research costs to incorporate gRoR by using this protocol, including laboratory verification of previously genotyped and sequenced samples, re-collection and CLC of new samples, as well as estimated salaries for program oversight and staffing (Figure 5).[42] Laboratory personnel costs and effort were estimated for generating genetic research results and for CLIA confirmation, while material costs were actual. Efforts by the team to review medical records, inform individuals about the research completed finding, and coordinate confirmatory testing and clinical disclosure sessions were estimated with a modified micro-costing approach[43] where time estimates of all logged contacts were multiplied by median national hourly costs for the relevant personnel and adjusted for wage inflation.[44] Fixed costs included office space and personnel costs, including monthly meetings of the 19-member MGB Biobank Return of Results Committee during a 46-month period, including monthly effort for committee leadership, and 3 months of committee time to establish the gRoR pipeline (e.g., protocol creation and IRB review). Cost analyses are presented in 2021 US dollars and include the costs associated with obtaining a second DNA sample and performing CLC of the second sample. Costs of the research GT/GS, the medical appointments for confirmatory variant disclosure, and subsequent costs for participant management were not included in these estimates.

Results

Participants

Between July 1, 2010 and March 31, 2021, the MGB Biobank enrolled 124,391 individuals, of whom 87,751 provided a blood sample. Beginning in 2015, DNA samples on 36,417 participants were genotyped with one of

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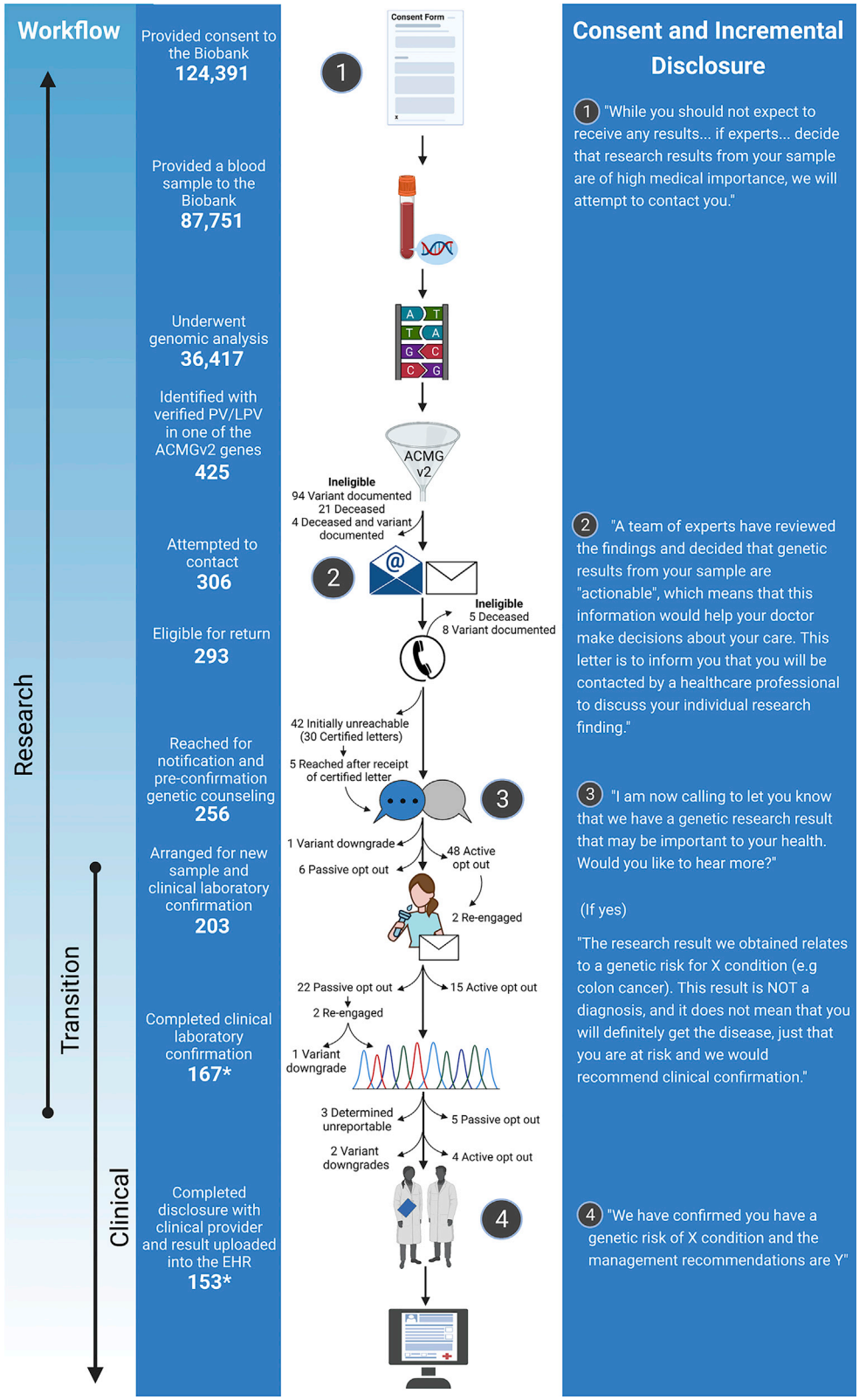

Figure 2. Participant flow through the biobank incremental disclosure gRoR process
Asterisks indicate that this number includes ten participants that have elected to proceed with gRoR and are in progress but have not completed it.

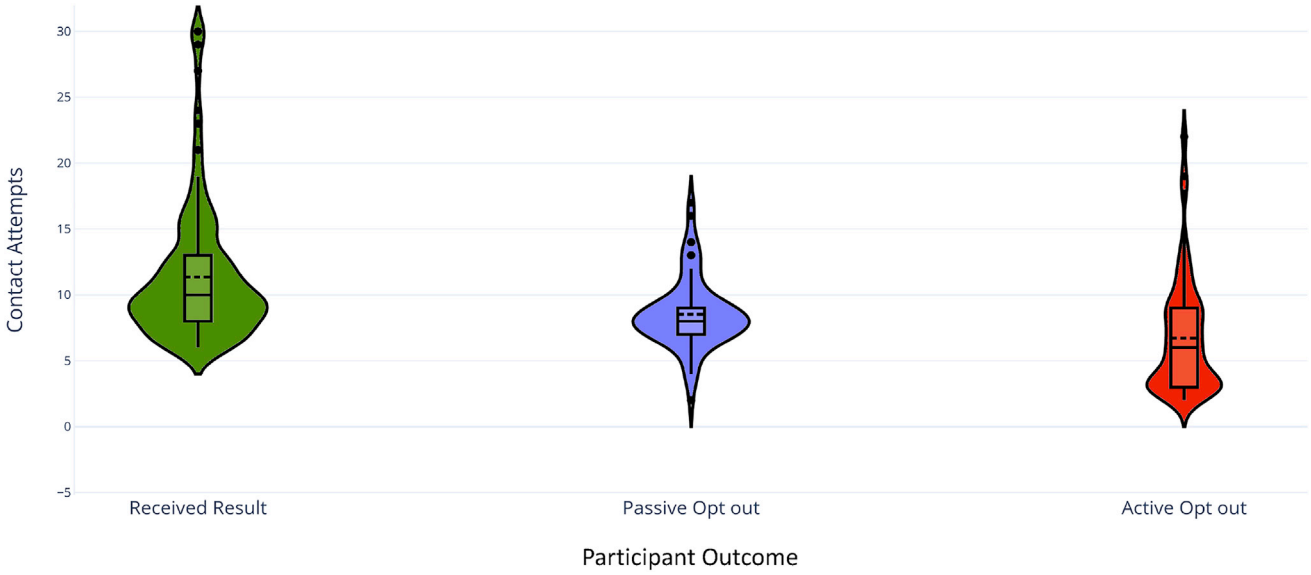

Figure 3. Number of contacts and contact attempts needed for each participant outcome
Participants are grouped into three kernel density plots that show the range of contact attempts needed to successfully disclose a result to participants (green) or to reach active (red) or passive (purple) opt out of the gRoR process. Also shown within each shape are boxplots and interquartile ranges where the mid-plot solid line indicates the mean and the mid-plot dashed line indicates the median. Outliers in each violin plot are indicated by dots and represent situations in which multiple contacts ("please call me back," "I'd like to think about it further") were needed before the participant agreed to progress to results disclosure, ceased responding (passive opt out), or finally declined to proceed (active opt out). This figure excludes in-progress participants.

Illumina's Multi-Ethnic Global arrays (see "Illumina Infinium Multi-Ethnic Genotyping array" in web resources) (Table 1, Figure 2). Two subsets of the samples that underwent GT also underwent genomic sequencing (GS): these samples were from (1) a cohort of 2,349 participants in whom a limited set of medically actionable genes was sequenced as part of the Electronic Medical Records and Genomics (eMERGE) III program[30] and (2) a cohort of 914 additional underrepresented minorities (Black or African American, Hispanic or Latino, or other) that were prioritized for analysis of exome sequencing. Table 1 shows the demographics of the participants in the MGB Biobank, those whose DNA was analyzed, those in whom returnable findings were identified, those who were eligible for results return, and those in whom results were disclosed or in whom disclosure is underway. Because genetic analysis and interpretation lagged behind consent and enrollment, participants were consented an averaged 3.4 years (range 1.8–8.9 years) before they were contacted for gRoR.

Participant contact

We tabulated the number of contacts required to notify participants of the research results, as well as the number of participant and provider contacts required to arrange for CLC and disclosure among those who elected disclosure, those who eventually opted out at any point (active opt out), and those who were reached but ceased responding to our calls (passive opt out) (Figures 2 and 3, Table 2). Of the 425 participants identified with actionable variants, we found 293 who were eligible for return after EHR review and initial contact attempts. We reached 256 (87%) of these for result notification and pre-confirmation genetic counseling, confirmatory sample collection was initiated for 203 (69%) individuals (192 saliva kits and 11 blood draws), results were confirmed by CLC and disclosed to 143 (49%) participants, and ten are currently in the process of confirmation (Figure 2, Table 2).

Research laboratory findings and verification

Variants from both GT and GS were filtered and classified to identify PLPVs in the ACMG v.2 genes for possible gRoR. Initial inspection of GT samples indicated a high proportion of false positive calls, so a Sanger verification step was performed on samples that yielded PLPVs by GT prior to participant contact. This verification step determined that 28.9% (63/218) of unique variants and 44.9% (302/673) of the samples were analytic false positives (Figure 1A). As expected, GS showed very high rates of verification.[45] A total of 425 unique participants had a PLPV identified in Sanger-verified GT or GS (Figure 2). PLPVs among the ACMG v.2 genes were found in 1.0% (368/36,417) of participant samples that underwent Sanger-verified GT and 2.5% (82/3,263) of those that also underwent GS. Detection of PLPVs in the GT data was limited to those variants/conditions present on the array, as compared to the unbiased GS data (Figure 1B). Among those participants whose samples underwent both GT and GS, there were 79 unique variants in 82 participants identified by GS, but 58 of these variants in 59 participants (72.0%) were missed by GT because of the absence of a probe on the array (45 unique variants) or because of poor performing or incorrectly annotated probes (13 unique variants) (Figure 1C).

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Table 2. Breakdown of participants with a lab reportable variant discovered by result type

	Cancer	Cardiac	FH	Other	Total
Number of participants identified with a lab reportable variant	**209**	**122**	**75**	**19**	**425**
Variant previously documented	43.1% (n = 90)	9.8% (n = 12)	2.7% (n = 2)	10.5% (n = 2)	24.9% (n = 106)
Deceased	8.1% (n = 17)	4.1% (n = 5)	8% (n = 6)	10.5% (n = 2)	7.1% (n = 30)
Eligible for return	50.7% (n = 106)	86.1% (n = 105)	89.3% (n = 67)	78.9% (n = 15)	68.9% (n = 293)
Result disclosed	29.7% (n = 62)	41% (n = 50)	26.7% (n = 20)	57.9% (n = 11)	33.6% (n = 143)
Variant downgraded during gRoR	0% (n = 0)	2.5% (n = 3)	1.3% (n = 1)	0% (n = 0)	0.9% (n = 4)
Number of participants eligible for gRoR	**106**	**105**	**67**	**15**	**293**
Unreachable	10.4% (n = 11)	12.4% (n = 13)	17.9% (n = 12)	6.7% (n = 1)	12.6% (n = 37)
Reached	89.6% (n = 95)	87.6% (n = 92)	82.1% (n = 55)	93.3% (n = 14)	87.4% (n = 256)
Number of participants reached	**95**	**92**	**55**	**14**	**256**
Opted out of return	31.6% (n = 30)	37.0% (n = 34)	52.7% (n = 29)	21.4% (n = 3)	37.5% (n = 96)
Active opt out	27.4% (n = 26)	19.6% (n = 18)	34.5% (n = 19)	14.3% (n = 2)	25.4%(n = 65)
Passive opt out	4.2% (n = 4)	17.4% (n = 16)	18.2% (n = 10)	7.1% (n = 1)	12.1% (n = 31)
Number of participants in which Sanger confirmation was attempted	**66**	**57**	**28**	**11**	**162**
Sanger-confirmed variants	98.5% (n = 65)	100% (n = 57)	92.9% (n = 26)	100% (n = 11)	98.1% (n = 159)
Variant not reportable after clinical Sanger sequencing	1.5% (n = 1)	0% (n = 0)	7.1% (n = 2)	0% (n = 0)	1.9% (n = 3)

Transitioning participants into the clinical workflow

Of 425 participants initially identified with PLPVs in the ACMG v.2 genes, EHR review or phone notification revealed that 30 (7.1%) were deceased, 106 (24.9%) were previously known to have the variant, including 4 that fell in both categories. A total of 256 eligible participants were reached for pre-confirmation counseling by the sGC, including four individuals whose variants were downgraded during the gRoR process and three individuals whose variants were determined to be unreportable during clinical confirmation (Figure 2, Table 2). Between two and 12 contact attempts were required to reach each participant for result notification and counseling, and between four and 28 additional contact attempts with participants and providers were needed to facilitate final result disclosure (Figures 2 and 3, Figure S1). Of the 256 participants who were alerted that they carried a medically important DNA change, there were a total of 65 active and 31 passive decliners. Four initial decliners re-engaged in the disclosure process, for a total of 96 participants who declined and an overall decline rate of 37.5% (Figure 2, Table 2). Comparing those who declined by category of underlying condition, there were 30 of 95 participants reached (31.6%) who declined after being alerted that they carried a variant for increased cancer risk, 29 of 55 participants reached (52.7%) who declined after being alerted that they had a variant for a hereditary high cholesterol disorder, 34 of 92 participants reached (37.0%) who declined after being alerted that they had a variant for a (non-FH) heart condition and three of 14 participants reached (21.4%) who declined after being alerted that they had a variant that would cause an abnormal reaction to surgical anesthesia (referring to *RYR1*) (Table 2). A subset of the decliners, consisting of 34 active and 17 passive decliners, were contacted to ascertain reasons for declining, and 17 and 7, respectively, completed a qualitative interview (Note S5). The most common reasons for declining confirmatory testing were that individuals perceived their genetic results to be irrelevant (largely because they were already aware that they had the associated phenotype) or that they had more pressing medical concerns (Figure S2). None of the participants who received notice of a medically important finding expressed distress about being alerted for potential gRoR or about the subsequent process of disclosure. Among those who elected to proceed with clinical confirmation and disclosure, it took an average of 88 days (median 56 days) from completed sGC notification to clinical result disclosure. Factors impacting this were how quickly participants provided a clinical sample for confirmation, time to generate the laboratory report, and disclosure appointment scheduling.

Comparison to established clinical criteria for genetic testing

The EHR was reviewed for 418 participants (the total with a variant identified excluding those downgraded during gRoR [n = 4] and those not reportable after Sanger confirmation [n = 3]). Of those living and deceased

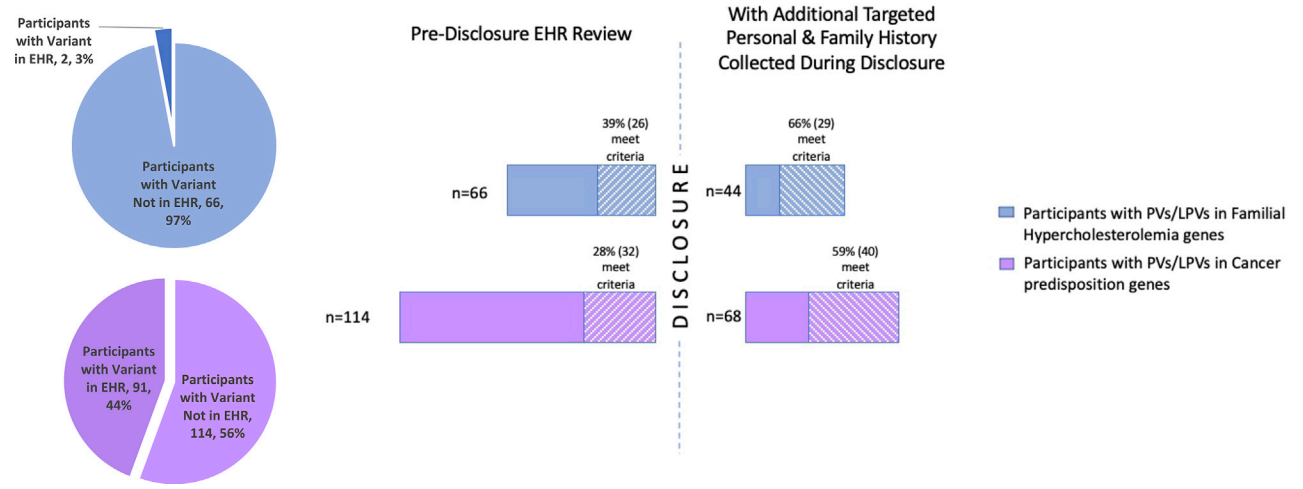

Figure 4. Electronic health record (EHR) review of those meeting professional guideline criteria for clinical genetic testing
EHRs were reviewed for participants with PLPVs in three familial hypercholesterolemia (FH, blue) genes and 22 cancer predisposition genes (purple). Pie charts reveal the percentage of individuals whose PLPV was previously documented in the medical record. Chart reviews were performed with NCCN guidelines or other established expert criteria for cancer predisposition syndromes and the Dutch Lipid Clinic Networks guidelines for FH. The bar graphs show the percentage of participants whose PLPV variant was not previously documented in the EHR but who nonetheless met expert criteria for ordering genetic testing on the basis of EHR review alone (pre-disclosure EHR review) and the percentage of participants who met expert criteria for ordering genetic testing on the basis of EHR review and additional personal and family history gathered from the participant in the process of disclosure.

participants who were found to have PLPVs in the ACMG v.2 genes, 319/418 (76.3%) did not have the variant previously documented in their EHR. We reviewed the EHR for documented medical and family history and assessed whether, prior to disclosure, 180 participants without documentation of prior genetic testing met available expert criteria to prompt genetic testing for their condition from the National Comprehensive Cancer Network (NCCN) for genetic testing for cancer (see Else et al. GeneReviews and van Leeuwaarde et al. GeneReviews in web resources)[36,37] or the Dutch Lipid Clinic Network (DLCN) criteria for FH, without awarding points for research discovery of the PLPV.[39,40] Among participants without documentation of prior genetic testing, 32/114 (28%) with PLPVs in cancer predisposition genes fulfilled NCCN guidelines for genetic testing and 26/66 (39%) of those with PLPVs in FH genes were considered "likely" to have FH by DLCN criteria based upon EHR review alone (Figure 4). After obtaining additional family history at the time of notification and disclosure in 112 of the 180 participants, these proportions increased to 40/68 (58.8%) for NCCN criteria and 29/44 (65.9%) for DLCN criteria (Figure 4).

Assessment of decisional regret

A decision regret scale[41] was administered as part of a larger survey at 1 and 6 months. Participants who completed the entire protocol and had their research result clinically confirmed and disclosed were asked how they felt about their decision to enroll in the study and receive results. At 1 month following disclosure, 57/111 (51.4%) responded to the survey, and only one individual scored in the range that suggested regret. The mean score was 8.8 on the 0–100 scale (in which higher scores indicate greater levels of regret), lower than observed in other studies of genetic disclosure to biobank populations.[46] At 6 months, 50/95 individuals (52.6%) responded to the survey with a mean score of 10.8 on the same scale, and only one individual (a different individual than the 1-month respondent, who did not complete a 6-month survey) scored in the range that suggested regret.

Time and budget impact analysis

Total costs for gRoR efforts with our protocol were estimated at $493,258, including $237,239 (48.1%) for screening and laboratory analysis, including initial verification and eventual CLC, and $136,574 (25.0%) for program oversight (Figure 5). Spread across the entire cohort of persons whose DNA was analyzed and the duration of the gRoR effort in the biobank, this represented approximately $14 per participant and approximately $129,000 per year. Genetic counselors and research assistants devoted 370 h from May 2017 through March 2021 contacting participants about their result, 35 h coordinating confirmatory testing, and 358 h coordinating clinical appointments for disclosure and subsequent care. Amortized across the 153 clinical disclosure sessions, each participant who eventually received disclosure in the clinical domain required 5.0 h of time by the sGC and research assistants and cost the overall research team and associated laboratory approximately $3,224.

Discussion

In this report, we describe the consent, recontact, analysis, yield, effort, and cost involved in analyzing research

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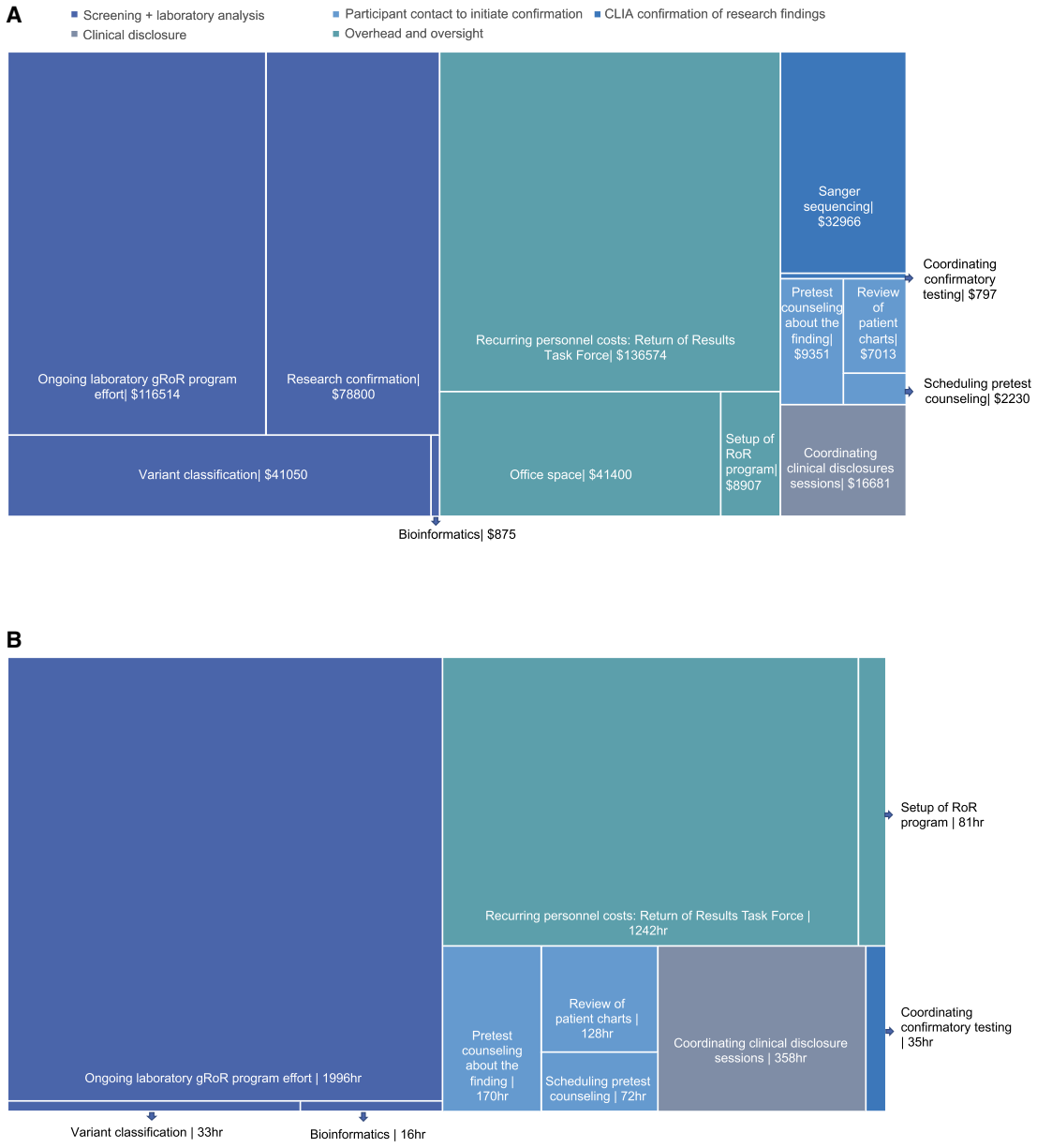

Figure 5. Cost and time impact analysis of gRoR to MGB Biobank participants
(A) shows a treemap of research cost (in 2021 US dollars), whereas (B) shows a treemap of research personnel time (in personnel hours) invested in analysis and subsequent gRoR across all biobank participants. Research-based confirmation and CLIA-based Sanger sequencing confirmation are accounted for as reagent costs only and hence do not have a time associated with them, whereas office space is accounted for as a fixed cost that did not change for the duration of the gRoR process and hence these metrics are not indicated in (B).

results for actionable genomic findings, confirming and disclosing these findings, and transitioning participants who learn these findings into clinical care. Our gRoR protocol is not proposed as a criterion standard for how gRoR should take place, but it provides details and insights that may assist other investigators in designing their own gRoR protocols. In particular, we document that 76.3% of individuals who carried actionable variants were unaware of this, and that between 59%–66% of those met available professional guidelines to prompt genetic testing but had never been tested. While the vast majority of research participants across multiple studies claim they wish to be alerted to genetic findings of medical importance,[1–3] 37.5% of those in our biobank who were contacted with such results actively or passively declined return of actionable results despite numerous contact attempts. In addition, we document a cost of $14 per participant, above and beyond the initial research genotyping or sequencing, to cover our gRoR protocol, resulting in an average cost of $3,224 for each participant for whom gRoR was successfully completed.

Given limitations in participant understanding of consent,[47,48] it is extremely challenging to effectively educate and counsel every biobank participant about each of the rare conditions that might be revealed with gRoR. Our protocol utilized an incremental disclosure process for gRoR in which participants were not asked to finalize their willingness to receive genetic results upon enrollment, but rather were consented to recontact if the investigators discovered medically important findings. Various alternative models for gRoR consent (generic, staged, mandatory, tiered-layered-staged) have been proposed,[49–51] but empirical data on these are scarce. Our approach shares some features with mandatory or staged consent models[51,52] and has the advantage of reducing complexity during initial consent by moving the counseling and decision about additional information and disclosure to the time frame in which the participant would actually utilize the information, which in our biobank was up to 9 years after enrollment. The fact that more than one-third of our participants actively or passively opted-out of further disclosure once alerted to the fact that they carried an actionable genomic finding would suggest that the incremental disclosure process did not compromise participants' freedom to decline full disclosure. And among those whom we could reach for follow-up inquiry, there was no distress recorded from those who opted out, nor any widespread regret among those who carried through to full disclosure.

Our data on the frequency of verified PLPVs among the ACMG v.2 gene list in biobank participants are consistent with prior population screening efforts using this list that yielded a frequency of such variants of 1%–1.5% among individuals who had been genotyped[53] and 2.6% among individuals who had been sequenced.[54–56] Our data replicate and extend prior observations around the poor performance of GT as a potential tool for biobank gRoR or population screening.[53,57–59] Of the initial GT calls from over 36,000 participants from our biobank, nearly 45% of samples initially identified as carrying PLPVs were false positives. And in the subset of 3,263 participants who had both GT and GS, GT failed to detect a PLPV in 72.0% of the participants who were carrying GS-detected PLPVs. The comparison of GT and GS data also demonstrates a bias in identifying variants in certain genes and conditions that were not part of the array designs. Aside from common variants in *BRCA1* and *BRCA2*, variants indicating cancer predisposition were considerably less well-detected in GT as compared to GS. This bias may be different in other arrays such as the Global Screening Array (GSA) that was specifically designed for population-scale genomic studies around monogenic disease, but a study of over 5,000 participants screened with a GSA in Alabama revealed very similar figures for the overall yield and for the rate of analytic false positives.[53] The limitations of GT are important to recognize as some healthcare systems and biobanks are already returning genomic results discovered through GT.[53,60–62]

Returning genomic results from the MGB Biobank and other research studies reveals that expert guidelines to prompt genetic testing are not being followed in clinical care. Among all of our biobank participants identified to carry verified PLPVs, the molecular diagnosis was previously documented in the EHR for less than one-quarter of participants. This was particularly striking because over half of those participants with previously unrecognized PLPVs associated with heritable cancers or lipid disorders that have clear guidelines for treatment met published professional criteria for genetic testing (see Else et al. GeneReviews and van Leeuwaarde et al. GeneReviews in web resources).[36,37,39,40] Expert clinical recommendations for genetic testing have not been translated into clinical care, as has been observed in other health systems.[23,63–66]

It is well recognized that the anticipated logistical and financial burdens of gRoR may discourage research biobanks from considering gRoR.[67,68] Setting aside the cost of the original research genotyping or sequencing, and ignoring downstream medical costs that might be triggered by the disclosure of the finding, the design, oversight, and implementation of our entire gRoR protocol, including laboratory verification of initial GT findings and coverage of CLC cost, was approximately $129,000/year over 4 years, representing about $14 per participant or $3,224 per participant in whom a verified and confirmed result was successfully disclosed. These figures contrast with $605 per participant-disclosure for gRoR for the return of six aortopathy genes[46] and $750 per participant-disclosure for a subset of the ACMG v.2 gene list in a pediatric biobank.[22] The difference in cost estimates may be because those studies did not actively screen for variants unrelated to participants' presenting diagnoses and omitted most overhead costs (34% of our total estimated costs). Our cost estimates did not include expenses to the healthcare system incurred during and after clinical disclosures, however, there is emerging evidence from economic models that genomic risk information may be cost-effective.[69–71]

Resampling participants for CLC is a routine part of gRoR in most US environments because research genotyping and sequencing is typically not conducted through a CLIA-approved laboratory process that asserts quality control along the chain of custody and within the laboratory itself, and there have been widely accepted assertions by the Centers for Medicare and Medicaid Services (CMS) that laboratory results generated in a non-CLIA process should not be disclosed to individuals.[72] But as shown in Figures 2 and 3 and Table 2, a substantial proportion of participants who were reached and informed that they carried a medically important variant actively or passively declined to complete the process, either before or after they submitted a second sample for confirmation of the research result. Some of these opt outs may have represented authentic decisions to avoid confronting a medical risk, but others may have represented insufficient

motivation to overcome the barrier of multiple communication steps with study staff or of submitting a new DNA sample.

There are a number of important limitations to this report. Our biobank recruited patients within an urban academic healthcare system. Like all gRoR models, ours depends upon the ability of biobank personnel to successfully recontact participants, and biobanks that aggregate participant data from multiple sites would face a different set of challenges.[73] Our interactions with participants through surveys and decliner interviews did not reveal regret over recontact and notification, but not all decliners were reached for interviews, not all who received a result completed a survey, and some that we did not reach could have been confused or distressed. As final disclosures were conducted in a clinical setting, this could present challenges to the uninsured or underinsured. The proportions of Hispanic or Black participants, though consistent with the proportions of participants in the biobank, were small, so our findings may not be applicable to participants in racial or ethnic groups that have experienced disparities, and additional research is needed in these populations.

While it is sometimes difficult to achieve consensus on what constitutes actionable genomic findings, it is clear that this category is expanding[74] and that there will be increasing interest in, and demand for, gRoR. Although planning for gRoR in a research biobank can be complex, we hope the results of this study illuminate lessons learned that can be considered by other groups seeking to find the balance between conducting scientific research, preserving participant autonomy and privacy, and offering information that could reduce morbidity and mortality among those who have generously contributed their DNA for the benefit of science.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2021.10.005.

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Declaration of interests

S.T.W. has received compensation from UpToDate. J.W.S. is a member of the Leon Levy Foundation Neuroscience Advisory Board and received an honorarium for an internal seminar at Biogen. He is PI of a collaborative study of the genetics of depression and bipolar disorder sponsored by 23andMe for which 23andMe provides analysis time as in-kind support but no payments. R.C.G. has received compensation for advising the following companies: AIA, Genomic Life, Grail, Humanity, Kneed Media, Plumcare, OptumLabs, Verily, and Vibrent Health. He is co-founder of Genome Medical.

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Web resources

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Supplemental information

Returning actionable genomic results in a research biobank: Analytic validity, clinical implementation, and resource utilization

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Returning Actionable Genomic Results in a Research Biobank: Analytic Validity, Clinical Implementation and Resource Utilization

Supplementary Appendix

Subject Identification

Protocol Title: **Partners HealthCare Biobank**
Principal Investigator: Scott T. Weiss, MD, MS

Description of Subject Population: Individuals seen at Partners HealthCare

1. What is the purpose of this research?

Researchers at Partners HealthCare System (Brigham & Women's Hospital, Massachusetts General Hospital, and other Partners institutions) are studying how genes and other factors affect people's health and contribute to human disease. To perform this research, we are asking patients at Partners to participate in the Partners HealthCare Biobank (Partners Biobank or Biobank) with blood samples to be stored in a research tissue bank (the "Biobank"). Taking part in this research study is up to you. Your decision to participate will not affect your clinical care in any way. Your participation can help us better understand, treat, and even prevent diseases that affect your loved ones, your family's future generations, as well as the larger community.

If you have any questions before you sign this consent form or after you join the study, you can contact the Partners Biobank staff at 617-525-6700 from Monday - Friday 9a – 5p. The person in charge of the Partners Biobank is Scott T. Weiss, MD. If you want to speak with someone **not** directly involved in the study, contact the Partners Human Research Committee at 857-282-1900. There is also an attached fact sheet that expands on the consent form to provide definitions and additional information.

2. What will happen in this study?

- You may be asked to donate a blood sample of up to 5 tubes (about 3 tablespoons). If blood samples for the Biobank are not collected today, they may be collected at a future time when you have a blood draw ordered by your doctor.We may also use blood, urine or tissue samples collected as part of your clinical care now or in the future that would otherwise be thrown away.
- We will also look at your medical records now and in the future to update your health information. We will store some of your health information in the study database.
- We may ask you to complete questionnaires about your health.
- We may contact you in the future to get additional information and ask if you are interested in joining other research studies.
- A notation that you are taking part in this research study may be made in your electronic medical record.

3. For what type of research will my samples be used?

- We plan to do many types of biological and genetic research with your sample, for example, research on heart disease, cancer, diabetes, mental illness, or reproduction to name a few. Genetic

research may include looking at some or all of your genes and DNA to see if there are links to different types of health conditions.

- We may create a "cell line" from your sample that will allow researchers to have an unlimited supply of your cells for research.
- We may use your cells to create pluripotent stem cells. This type of cell can be used to create different types of tissue, for example, heart, muscle, or lung cells. Your cells might be used in research that alters genes in the cells in order to study different diseases and normal healthy processes. Your cells might be mixed with other human cells, animal cells, or grown in lab animals like mice.
- We may share your samples and any cell lines that are created, your DNA sequence information, your health information, and results from research with other central tissue or data banks, such as those sponsored by the National Institutes of Health, so that researchers from around the world can use them to study many conditions.

4. Will I get results of research done using my samples?

- You may receive a newsletter or other information that will tell you about the research discoveries from the Biobank. This newsletter will not identify you or describe any of your personal results. It may be sent via Patient Gateway email if you're on Patient Gateway, by unencrypted email to your email address if you gave us one, or by US mail to your home address.
- Generally, we will not return individual results from research using your samples and data to you or your doctor. Research using your sample is just a stepping stone in learning about health and disease. Most of the findings that come from studying your sample will not be relevant to your personal health. However, in the future, this may change.
- It is important to remember that research results are not always meaningful and are not the same as clinical tests. While you should not expect to receive any results from your participation in this research, if experts from the Biobank decide that research results from your sample are of high medical importance, we will attempt to contact you. In some situations, follow up testing might be needed in a certified clinical lab. You and your medical insurer may be responsible for the costs of these tests and any follow up care, including deductibles and co-payments.
- It is possible that you will never be contacted with individual research findings. This does not mean that you don't have or won't develop an important health problem.
- In the future, when research results are published, they may show that certain groups (for example, racial, ethnic, or men/women) have genes that are associated with increased risk of a disease. If this happens, you or others may learn that you are at increased risk of developing a disease or condition.

Subject Identification

5. What are the benefits to me? Will I be paid for my samples?

- You will not directly benefit from research conducted on your samples stored in the Biobank. We hope that research using the samples and information will help us understand, prevent, treat, or cure diseases.
- You will not receive payment for your samples. In some locations, your parking cost may be covered or you may receive a cafeteria voucher.

6. What are the costs to me to take part in the research tissue bank?

There are no costs to you to participate in the Biobank.

7. How are my samples and health information stored in the Biobank?

Staff at the Biobank will assign a code number to your samples and health information. Your name, medical record number, or other information that easily identifies you will not be stored with your samples or health information. The key to the code will be stored securely in a separate file.

8. Which researchers can use my samples and what information about me can they have?

- Your coded samples and health information may be shared with researchers at Partners institutions. They may also be shared with researchers at non-Partners institutions or with for-profit companies that are working with Partners researchers. Your samples will not be sold for profit. We may use your samples and information to develop a new product or medical test to be sold. The hospital and researchers may benefit if this happens. There are no plans to pay you if your samples and information are used for this purpose.
- We will only share information that identifies you with researchers within Partners who have approval of the Partners ethics board. We will not share information that identifies you with researchers outside Partners.
- In order to allow researchers to share research results, agencies such as the National Institutes of Health (NIH) have developed secure banks that collect and store research samples and/or data from genetic studies. These central banks may store samples and results from research done using Partners Biobank samples and health information. The central banks may share these samples or information with other qualified and approved researchers to do more studies. Results or samples given to the central banks will not contain information that directly identifies you. There are many safeguards in place at these banks to protect your privacy.

9. How long will the Biobank keep my samples and information?

We will store your samples and information indefinitely.

10. Can I stop allowing my samples and information to be stored and used for research?

Yes. You can withdraw your permission at any time. If you do, your samples and your information will be destroyed. However, it will not be possible to destroy samples and information that have already been given to researchers. If you decide to withdraw please contact the Partners Biobank staff in writing. In case we need to contact you about medically important research results from your sample, please notify the Partners Biobank staff if your address changes.

Partners Biobank 65 Landsdowne St, Room 142 Cambridge, MA 02139	Phone: 617-525-6700 FAX: 617-768-8513 Email: biobank@partners.org

11. What are the risks to me?

- The main risk of allowing us to use your samples and health information for research is a potential loss of privacy. We protect your privacy by coding your samples and health information.
- There is a risk that information about taking part in genetic research may influence insurance companies and/or employers regarding your health.
- Research results obtained in this study will not be placed in your medical record unless we contact you with an important finding and you agree to have it confirmed. We do not think that there will be further risks to your privacy by sharing your samples and/or whole genome information with other researchers; however we cannot predict how genetic information could be used in the future.
- There is a very small risk of bruising or infection from drawing blood similar to what might occur from a routine blood draw that you get for your doctor.

12. If I take part in the Biobank, how will you protect my privacy?

In general, health information that identifies you is private under federal law. However, you should know that in addition to Partners researchers the following people or groups may be able to see, use, and share your identifiable health information from the research and why they may need to do so:

- Any sponsor(s) of this Biobank and the people or groups it hires to help with the Biobank
- The Partners ethics board that oversees the project and the Partners research quality improvement programs
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or organizations that we hire to do work for us, such as data storage companies, insurers, and lawyers

Subject Identification

- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- We share your identifiable health information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside Partners, we cannot promise that it will remain private.

13. Certificate of Confidentiality for Health Information and Other Identifying Information from the Research

To help protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. Researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation for Federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

A Certificate of Confidentiality does not prevent researchers from voluntarily disclosing information about you, without your consent in incidents such as child abuse, and intent to harm yourself or others.

Informed Consent and Authorization for Collection of Samples and Health Information for Research

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research study to the subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time

Subject Identification

Signature of Subject: I give my consent to take part in this research study and agree to allow my samples and health information to be used and shared as described above.

_____ _____ _____

Subject Date Time

_____

Email

Note S2: Letter Informing Participant of Actionable Result

Partners HealthCare Biobank

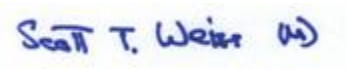
Dear Mr./Ms. (*Name*),

Thank you for participating in the Partners HealthCare Biobank (Partners Biobank) project at (*Massachusetts General Hospital* OR *Brigham and Women's Hospital*). Researchers using your samples have made discoveries that may be important to your health. A team of experts have reviewed the findings and decided that genetic results from your sample are "actionable", which means that this information would help your doctor make decisions about your care.

This letter is to inform you that you will be contacted by a healthcare professional to discuss your individual research finding. Research findings are not the same as clinical tests done during routine clinical care. Your doctor may want to repeat the research test using a certified clinical laboratory to be certain that the result is correct. The costs for repeating these tests will be billed to your insurance. You can decide whether or not you want the healthcare professional to contact your doctor with your health-related research finding.

If you have any questions about this letter, or about the Partners Biobank study, please contact the Partners Biobank staff by phone at (617-525-6700), or email at (biobank@partners.org). If you would like more information about the Partners Biobank, you may also visit our website at www.partners.org/biobank.

Sincerely,



Scott T. Weiss, MD, MS
PRINCIPAL INVESTIGATOR

PARTNERS HEALTHCARE | BIOBANK

Return of Research Results Phone Scripts

Contents

PARTNERS HEALTHCARE | BIOBANK

Voicemail Message

Hello. This message is for Mr./Ms. (*Name*). My name is [name of genetic counselor] and I am calling from Mass General Brigham.

I am calling with regard to your participation in a research project at (*Massachusetts General Hospital* OR *Brigham and Women's Hospital* OR *Spaulding Rehabilitation Hospital* OR *McLean Hospital*).
Please contact me at [genetic counselor email] or by telephone at [genetic counselor phone].

Have a great day. Goodbye.

PARTNERS HEALTHCARE | BIOBANK

Pre-Test Counseling Phone Call

Checklist

Name of Subject	
Subject ID	
Date of Pre-Test Counseling Phone Call	
Name of GC	

- ☐ Communicate disease name and description of disease associated with the variant
- ☐ Communicate loss of confidentiality
- ☐ Communicate social and economic disadvantages (impact on insurance)
- ☐ Communicate potential impact on family
- ☐ Communicate cost
    - ☐ Specify that cost of clinical visit to receive result will be billed to patient, but clinical validation will not
- ☐ Review sample collection process: option to do blood draw or saliva kit
    - ☐ If saliva kit, confirm address and phone number to ship kit
    - ☐ If blood draw, schedule visit at CCI
- ☐ Record preference to receive result: apt with MG or HCP
    - ☐ If preference is appointment with MG, we will coordinate with the MG team once the saliva kit has been received by the lab.
    - ☐ If preference is appointment with HCP, ask for the name and contact information for the HCP. This information will be included on the authorization form for the subject to sign. When the patient sends in saliva kit, we will begin to coordinate with the HCP.

PARTNERS HEALTHCARE | BIOBANK

Phone Scripts

GC:

Hello Mr./Ms. (*Name*), my name is [name of genetic counselor] and I am calling from (*Massachusetts General Hospital* OR *Brigham and Women's Hospital* OR *Spaulding Rehabilitation Hospital* OR *McLean Hospital*).

I am calling with regard to your participation in the Mass General Brigham Biobank project at (*Massachusetts General Hospital* OR *Brigham and Women's Hospital* OR *Spaulding Rehabilitation Hospital* OR *McLean Hospital*). Do you remember joning the Biobank?
If Yes: Procede with below script
If No: The Biobank is a reseach study that you joined to help scientistis learn more about your health. You would have signed a consent form and donated some blood at some point over the last several years.

As part of your consent to participate in the Biobank, we informed you that we would attempt to contact you in the event that research results from your sample might be medically important. I am now calling to let you know that we have a research result from your DNA sample that may be important to your health.

At this point, you have an option to hear more information about this research result, or decline to receive any additional information about the result. If you choose to hear more information about the result, you are still able to decline to receive additional information at any time, for any reason.

Would you like to receive more information about this research result from your DNA sample?

Subject:

Yes

GC:

The research result we obtained relates to a genetic risk for <insert disease name and description of disease>. This result is NOT a diagnosis, and it does not mean that you will definitely get the disease. At this point, the result only suggests that you may be at risk.

This preliminary research result will require verification in a separate clinical laboratory possibly with a new sample that we can typically get from saliva to confirm that the result is correct. In rare cases, we may need a blood sample if we cannot get enough DNA from

the saliva sample. Because this research result was discovered using a non- clinically approved test, it is not recommended that action is taken as a result of this research result at this time, which is why another test must be performed to verify that the result is correct.

Do you feel like you understand what we have discussed so far? Do have any questions at this time?

Subject:

Yes/No

If No, I do not understand:

GC:

Your result was identified as part of a study in a research setting. The standards followed for testing samples may vary among research laboratories. Clinical laboratories are held to higher standards when examining and reporting results and must meet quality standards set by the Clinical Laboratory Improvement Amendments (CLIA). Because of this we must collect a second sample and perform clinical grade testing to be sure the research result we identified is accurate.

If Yes, I understand:

GC:

Based on this preliminary research result, I recommend that you receive clinical genetic testing to verify the research result.

However, before you make a decision to receive clinical genetic testing, I need to review some important information with you. You will have the option to decline receiving the clinical genetic testing after we review this information.

If the result is clinically confirmed, specific screening, tests, exams, or lifestyle changes may be recommended for early detection and/or disease management. Knowing about a genetic risk variant could also be useful for future financial and/or family planning.

At the moment this variant is a research result and should not be placed in your medical record. However, once you result is clinically confirmed your disclosing provider will note it in medical record and the lab will upload this into your MassGeneral Brigham medical record. This result is also noted in your Mass General Brigham Biobank study record. This means that anyone who has access to your medical record will be able to see your genetic test result, like your other doctors.

As with any information going into your medical record, there is always a potential risk of **loss of confidentiality**. However, we do everything we can to keep your information safe.

Do you feel like you understand the potential loss of confidentiality? Do you have any questions?

Subject:

Yes/No

If yes, GC proceeds to next point.
If no, refer to standard questions and answers at the end of this document.

GC:

The second implication concerns potential risk of insurance discrimination. There is a federal law called GINA, which stands for the Genetic Information Non-Discrimination Act, that protects a person from discrimination based on their genetic information in employment and health insurance, but GINA does not provide protection in all situations. In most states, genetic discrimination laws do not currently protect a person from discrimination in life, long-term care, or disability insurance based on genetic information; however, in Massachusetts there are some state laws that offer additional protections. [If asked to elaborate- there must be actuarial evidence to present]. The risks of discrimination are not fully known, but it is possible that an individual known to have a genetic risk factor may have trouble obtaining or keeping life, long-term care, or disability insurance this could potentially cause you **social and economic disadvantages**.

Do you have any questions about the potential risk that the clinical validation could have in terms of access to life, long-term care, or disability insurance?

Subject:

Yes/No

If yes, GC proceeds to next point.
If no, refer to standard questions and answers at the end of this document.

GC:

The third implication concerns the potential **impact on your family**. Through clinical genetic testing, you may learn that other family member(s) are at risk for the same condition. Your relatives may or may not want to know this information. [GC to collect additional relevant family history to contextualize the result to their individual family history].

Do you have any questions about the potential impact on your family?

Subject:
Yes/No

If yes, GC proceeds to next point.
If no, refer to standard questions and answers at the end of this document.

GC:

The fourth implication is **cost**. There are costs associated with genetic testing. The cost of the sample collection and the test in the clinical laboratory are covered by the Biobank study as long as the test is done at the Laboratory for Molecular Medicine that is affiliated with the Biobank. If the test is done at another laboratory, you and your insurance will need to cover the cost. Once your result is clinically confirmed we recommend you see a doctor to review the implications of your clinical test result and what this means for your health. This doctors visit, typically with a medical geneticist or specialty provider with expertise in genetics, is NOT covered by the study but will be billed to your insurance.

If you or your doctors request follow-up care including medical tests or office visits to follow up on results found in the genetic testing, you may be responsible for these costs; however, these clinical interactions are often covered by health insurance. You or your relatives may be responsible for costs associated with additional testing to learn more about genetic variants that could affect the health of the patient's family.

Do you have any questions about the costs associated with the clinical validation?

Subject:
Yes/No

If yes, GC proceeds to next point.
If no, refer to standard questions and answers at the end of this document.

In order to move forward with the clinical validation, all we would need to do is

CLIA sample:
retest a sample of the blood that you already provided to the Biobank. The results of the genetic test should be ready in approximately 3-4 weeks.;

Non-CLIA sample:
We will mail you a saliva kit. You will follow the directions included with the tube to collect the saliva and will ship the sample back to us (postage is provided). In very rare cases, we may request that we collect an additional blood sample (if we cannot collect enough DNA though the saliva test).

If you would prefer to provide a blood sample, we can schedule a blood draw with MGH or BWH phlebotomy. In case you chose to do the blood draw, you will need to come into Brigham and Women's Hospital or Mass General Hospital. There will be no cost to you for the blood draw.
The results of the clinical genetic test should be ready in approximately 3-4 weeks.[Note for particularly anxious participants: "We can ask the lab to rush your sample and it should be ready in about 2 weeks, unless they experience lab issues).

Would you like to move forward with the clinical genetic testing?

Subject:

Yes/No

GC:

If No:

If No: Thank you for your time. We will send you a survey by mail or email to collect your feedback on our return of research results process. We may also call you to learn more about your decision making and experience. However, if you change your mind, you may contact Mass General Brigham Biobank staff for general questions by phone at (617-525-6700) or email at (biobank@partners.org). We will send you a survey. Goodbye.

If Yes:

GC:

CLIA sample: skip to next section ("Meet with MG/Meet with PCP")

Non CLIA sample:

Saliva sample:
next step is for me to make sure that we send you a saliva kit. Can you please confirm your address and phone number? We will send the saliva kit by fedex or ups. If you do not receive it in the next few days, please contact the Biobank at 617-525-6700 or email (biobank@partners.org) so that we may help you.

Blood sample:
OK, the next step is for me to schedule you to come into the Center for Clinical Investigation at Brigham and Women's Hospital or at the Mass General Biobank phlebotomy desk for the clinical blood draw. When would be a good time for you to come in?
<schedule appointment>

Once the test is complete, you will need to meet with a doctor to learn the genetic result. We strongly suggest that you meet with a Medical Geneticist or a specialist with

expertise in genetics to review your result and what it means for you and your family. We can help set this up for you. We can also share the result with your HCP if you would like. We will ask you to sign a medical relase form that indicates the doctor(s) you want us to share this information with. We will send this to you with your saliva sample.

If you agree to have your testing done at the MassGeneral Brigham LMM lab, we will also send you a clinical consent form that overviews the fact that you are obtatining a clinical test. We will ask you to sign this and send back with your saliva sample.

[In circumstances where the patient does not want to see genetics, or does not want to come into the city or to a location where there is an available medical genetics provider] If you prefer, you are also welcome to set up an appointment with your Primary Care Physician or other specialty physician. If this is your preference we will ask your permission to speak to your doctor and ask you to sign a medical release so we can share your result with them and we will ask your doctor if he/she is willing to review the results with you. If they do not feel comfortable reviwing these results with you we can help set you up with a specialist. If you agree to have your testing done at the MassGeneral Brigham LMM lab, we will also send you a clinical consent form that overviews the fact that you are obtatining a clinical test. We will ask you to sign this and send back with your saliva sample.

Would you like to meet with a Medical Geneticist/ Specialist with expertise in genetics [or with your HCP]?

Subject:

Meet with MG/ Specialist vs Meet with HCP

If meeting with MG, schedule meeting with MG/specialist to be when the results are available. Contact the MG/specialist GC and/or scheduling team to set this up.

GC:

Great. I can schedule a meeting with our Medical Geneticist/specialist for 3-4 weeks from when the lab receives your sample. This will give us enough time to obtain your sample and complete the test.

GC:

Great I will send you a medical records release form so that I can talk about and share the test result with your HCP. Once the lab has confirmed your result we will reach out to your HCP to let them know you need to be seen and they should contact you to set up an appointment.

After your results are disclosed you will receive a survey by email or mail asking you questions about participating in the biobank process. We would greatly appreciate you filling out this survey.

GC:
Do you have any questions at this time?

GC:
If No: Alright. Thank you for your time. Goodbye.

If Yes, GC answers questions or documents questions to discuss in in-person appointment.

Standard Questions and Answers

Responses to likely questions are as follows. If the participant does not ask these questions over the phone, these will be discussed at the in-person appointment:

Subject: What did you find? Why can't you tell me now?
GC: The genetic change/variant identified has been associated with an increased risk for <disease name and description of disease>. Since this research result was not discovered using a clinical genetic test, it is not recommended that any action be taken as a result of this research result at this time. We can assist you in having your variant confirmed in the Mass General Brigham Healthcare clinical laboratory

Subject: Does this mean I have a disease? Or will I definitely get the disease?
GC: We are returning results to individuals to whom we believe there is may be an increased risk of developing the particular condition. This does not mean you will definitely get the disease. It also depends on other factors such as your age, lifestyle, family history, environment, etc. And we do not know that the research result is correct which is why you would need to have a clinical test to confirm the result.

Subject: How can I make a decision about clinical testing if I don't know what you found?
GC: The genetic variant identified may be associated with an increased risk for <disease name and description of disease>. We are informing you about this result since there are guidelines available for screening and ways to lower your risk (if relevant). If you wish to proceed, after the result is confirmed using a clinical genetic test, a medical geneticist/genetic counselor can meet with you and provide you with specific recommendations about your risk, screening and management.

Subject: What are the costs of clinical genetic testing?
GC:

- Confirming your result using the Mass General Brigham clinical lab would not cost you anything.
- If you or your doctor request medical tests to follow up on results found in the genetic testing, you may be responsible for some of these costs. This may include the cost of additional testing to learn more about genetic variants that could affect the health of your family. To be clear, initial research result confirmation testing will be done at no cost to you, however, if there is follow-up clinical care and additional office visits, costs associated with continued clinical care (e.g. visit co-pays) will be your responsibility.

Subject: What are the potential benefits to me?
GC:

- Learning about your result may help your doctors make decisions about your medical care; for example, your doctors may recommend specific screening, tests, exams, or lifestyle changes to follow-up on the clinical test result or other conditions. Knowing about a genetic change could also be useful for your future financial and/or family planning and there may be potential benefit to your family members.

Subject: What are the potential risks?
GC:

- Loss of confidentiality
  Your clinical test result (from the confirmatory testing) will be placed in the electronic medical record as with anything in the medical record there is a potential loss of confidentiality but we do everything we can to keep your information safe and secure. We will not place the research result in the electronic medical record.

- Insurance
  There are laws (GINA) that protect a person from discrimination based on their genetic information in employment and health insurance, but they do not provide protection in all situations. In some states, these laws do not currently protect a person from discrimination in life or disability insurance based on genetic information. The risks of discrimination are not yet known, but it is possible that you may have trouble obtaining or keeping life or disability insurance.

- Impact on families
  You could also learn that other family member(s) are at risk for the same condition. Your relatives may or may not want to know this information.

Survey Reminder Phone Scripts

Phone Reminder

Hello Mr./Ms. (*Name*), my name is [name of Biobank staff] and I am calling from (*Massachusetts General Hospital* OR *Brigham and Women's Hospital* OR *Spaulding Rehabilitation Hospital* OR *McLean Hospital*).

I am calling with regard to your participation in the Mass General Brigham Biobank. As part of your consent to participate in this study, you agreed to be sent a few surveys. This is just a reminder to please complete the survey we recently sent you as soon as you can *[For the Baseline survey only- This is just a reminder to please complete the survey prior to your result disclosure visit.]*

Thanks for your time today.

Voicemail Message

Hello. This message is for Mr./Ms. (*Name*). My name is [name of Biobank staff] and I am calling from (*Massachusetts General Hospital* OR *Brigham and Women's Hospital* OR *Spaulding Rehabilitation Hospital* OR *McLean Hospital*).

I am calling with regard to your participation in a research project at (*Massachusetts General Hospital* OR *Brigham and Women's Hospital* OR *Spaulding Rehabilitation Hospital* OR *McLean Hospital*).
Please contact me at telephone at [staff phone].

Have a great day. Goodbye.

Note S4: Example Clinical Report

PARTNERS HEALTHCARE | PERSONALIZED MEDICINE

MASSACHUSETTS GENERAL HOSPITAL | BRIGHAM AND WOMEN'S HOSPITAL

Laboratory for Molecular Medicine
65 Landsdowne Street, Cambridge MA 02139
Phone: (617) 768-8500 Fax: (617) 768-8513
www.partners.org/personalizedmedicine/lmm

Unit Number(s):

Lab Accession:
Patient Name:
Birth Date:
Age Sex:

MOLECULAR DIAGNOSTICS REPORT

Specimen Type:
Related Accession(s):
Referring Physician:
Copies To:

Received Date:
Referring Facility:
Referring Fac. MRN:
Lab Control Number:
Family Number:

TEST DESCRIPTION – Clinical Confirmation Test - Partners Healthcare Biobank RoR
TEST PERFORMED – ClinCon-f
INDICATION FOR TEST – Partners Biobank Variant Confirmation

RESULTS
DNA VARIANTS:
Heterozygous c.10580G>A (p.Arg3527Gln), Exon 26, APOB, Pathogenic

INTERPRETATION:
Positive. DNA sequencing identified the variant listed above. This variant was previously identified by the Partners Biobank research study.

INTERPRETATION SUMMARY:
A well-established, heterozygous pathogenic variant in the APOB gene was identified in this individual. Pathogenic variants in APOB are associated with familial hypercholesterolemia (FH); therefore, this individual is at risk for developing hypercholesterolemia. Please note that pathogenic variants in APOB can have reduced penetrance and a less severe phenotype than disease causing LDLR or PCSK9 variants (Youngblom and Knowles, GeneReviews). The available information on this variant is described in the variant interpretation section below.

Disease penetrance and severity can vary due to modifier genes and/or environmental factors. The significance of a variant should therefore be interpreted in the context of the individual's clinical manifestations.

This test is variant specific and does not detect other variants in this gene or other genes.

INHERITANCE PATTERN:
FH due to pathogenic variants in the APOB gene is inherited in an autosomal dominant pattern. Each first-degree

MOLECULAR DIAGNOSTICS REPORT

relative has a 50% (or 1 in 2) chance of inheriting a variant and its risk for disease. Additional family members may also have inherited this variant and may be at risk for disease.

VARIANT INTERPRETATION:

p.Arg3527Gln, c.10580G>A (APOB; NM_000384.2; Chr2 g.21229160C>T; GRCh37):

The p.Arg3527Gln variant in APOB is a well-established pathogenic variant that is mainly found in individuals of European descent. It has been previously reported in >500 individuals with familial hypercholesterolemia (FH) and segregated with disease in >50 affected relatives (Soria 1989, März 1993, Leren 1997, Ludwig 1990, Bednarska-Makaruk 2001, Horvath 2001, Kalina 2001). It has also been reported by other clinical laboratories in ClinVar (Variation ID 17890) and has been identified in 53/126056 of European chromosomes, including 1 homozygote, by the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/; dbSNP rs5742904). This frequency is low enough to be consistent with the frequency of FH in the general population. In summary, this variant meets criteria to be classified as pathogenic for autosomal dominant familial hypercholesterolemia based upon presence in multiple affected individuals and segregation studies. Please note that pathogenic variants in APOB can have reduced penetrance and a less severe phenotype than disease-causing LDLR or PCSK9 variants (Youngblom and Knowles, GeneReviews). ACMG/AMP Criteria applied: PS4_Strong; PP1_Strong.

RECOMMENDATION:

Genetic counseling is recommended for this individual and her relatives. Familial variant testing is available for other relatives if desired. For assistance in locating genetic counseling services or disease specialists please call the laboratory at 617-768-8500 or email at LMM@partners.org. Please note that variant classification, particularly of uncertain significance, may change over time if more information becomes available. Please contact us at 617-7688500 or LMM@partners.org.

COMMENTS:

An online research opportunity called GenomeConnect is available for any recipient of genetic testing to advance knowledge of genetic variants by sharing de-identified genetic and health information. Please visit genomeconnect.org to learn more.

TEST INFORMATION BACKGROUND:

Clinical confirmation testing is performed to assess an individual's risk for developing or being a carrier of a genetic condition, determine if a variant has occurred de novo, determine cis or trans configuration, or to help clarify the significance of a variant through segregation studies. An individual's risk of disease depends on several factors, including the interpretation of the variant, penetrance and inheritance of the disease, presence of other variants, as well as other genetic and environmental factors.

METHODOLOGY:

Clinical confirmation testing is performed by Sanger sequencing of the variant(s) in the patient. This method is over 99.9% accurate. Testing may include specialized methods to address technically difficult genomic regions. Variant classifications are based on ACMG/AMP criteria (Richards et al. 2015) with ClinGen rule specifications

MOLECULAR DIAGNOSTICS REPORT

(https://www.clinicalgenome.org/working-groups/sequence-variant-interpretation/). Variants are reported according to HGVS nomenclature (www.hgvs.org/mutnomen). This test was developed and its performance characteristics determined by the Laboratory for Molecular Medicine at Partners Healthcare Personalized Medicine (LMM, 65 Landsdowne St, Cambridge, MA 02139; 617-768-8500; CLIA#22D1005307). It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

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Ludwig EH, McCarthy BJ. 1990. Haplotype analysis of the human apolipoprotein B mutation associated with familial defective apolipoprotein B100. Am. J. Hum. Genet. 47(4):712-20. PMID: 1977310.

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Youngblom E, Knowles JW. 1993. Familial Hypercholesterolemia in GeneReviews(®). Seattle (WA): University of Washington, Seattle. PMID: 24404629.

REPORT PREPARATION by
REPORT by
Final Diagnosis by

Biobank ROR Decliner Interview Guide

Hello, Mr./Mrs. _____. My name is XX and I am calling from the Partners Biobank at Brigham and Women's Hospital. You were previously contacted by the biobank in (month, year) about your research genetic test results. At that time, you did not want to pursue this information further and have these results confirmed by a clinical laboratory. The biobank staff supports any decision that participants make, and I am reaching out to you today to try to better understand how participants make these decisions about receiving or not receiving their genetic results. If you are willing, I would like to interview you for about 20-30 minutes.

Would you be willing to participate?

If they respond yes:

The purpose of this interview is to hear your thoughts about your decision to not receive your genetic test results. There are no right or wrong answers to these questions. We just want to better understand what our biobank participants think about when faced with this decision. This interview will be audio recorded and then later written out on paper to be analyzed. All identifying information will be removed in the paper version and all of the analyzed data will remain anonymous. I am going to begin the recording now.

This interview will last about 20-30 minutes. For participating in this interview, we will send you a $15 Amazon gift card as a thank you for your time. Your participation in this interview is completely voluntary and if at any point you wish to stop the interview, you are welcome to do so. Additionally, if there is a question you would rather not answer, just let me know.

Do you have any questions before we get started?

1. Can you tell me a little bit about the reasons why you declined to receive your genetic result?
    - **If a participant endorses one of the reasons below, can consider the prompt questions**
    - Did not want to provide another sample
    - Logistics/ Time Commitment
    - Anxiety of receiving results
    - Anxiety of waiting for results (**prompt:** Did you feel that waiting for the result would lead to more anxiety?)
    - Overwhelmed (not a good time) (**prompt:** Were there too many other things that were going on at the time that you were initially contacted?)
    - Simply not interested

- Concerned about confidentiality of test results (**prompt:** Could you say a little more about these concerns? Who were you worried would learn the information? Why were you worried?**)**
- Concerned about potential to receive unfavorable results (**prompt:** Could you say a little more about these concerns?)
- Concerned about genetics test report in medical record (**prompt:** If you could have chosen whether or not your genetic test result would be put into your medical record, would you have decided to receive your genetic result?)
- Religious or spiritual reasons (**prompt:** Did your religious or spiritual believed lead you to decline receiving your genetic results?
- Concerned about insurance discrimination (**prompt:** Were you worried about your genetic results impacting your insurance coverage?)
- Other (**prompt:** Were there any other factors that you considered when deciding not to receive your genetic test results?)

2. **If they endorsed "concerned about confidentiality of test results":** If you could have chosen whether or not your genetic test results would be put into your medical record, would you have decided to receive your genetic result?

3. Please share with me what you remember about donating a blood sample to the Partners biobank?
    - Can you tell me a little bit about why you decided to donate a sample?
    - Did you know that genetic testing might be performed on your sample?
        i. **If yes:** Did that knowledge influence your decision to provide a sample to the biobank?
        ii. **If no:** What was the main reason you decided to join the biobank?
    - **If they do not remember providing a sample:** You enrolled in the biobank during a visit to (Clinic they were enrolled at) and donated a sample for research, does that appointment help you recall joining?

4. (If participant recalls joining) When you enrolled in the biobank, what were your expectations in terms of hearing back about any results they might find?
    - (For both people who recall enrolling and those who don't): what was your initial reaction to being contact by the Biobank about a potentially actionable result related to the sample you provided?

5. To remind you, someone with the biobank contacted you about genetic testing results. Do you remember what condition these results were related to?
    - If **yes:** How familiar are you with this condition?
    - If **No:** The biobank contacted, you with genetic test results related to ____ condition. How familiar are you with this condition?
    - Can you tell me a little bit about the experiences you have had with this condition?
        i. Do you yourself have any symptoms of this condition like (describe symptoms specific to the condition)
        ii. Do you have any family members with this condition? If so, who?

iii. Do you know of anyone else in your life with this condition?
iv. What are your general thoughts about the condition?

6. When you spoke to the biobank genetic counselor, you told her were not interested in having your genetic result confirmed by a clinical laboratory. Do you remember making that decision?

- Did any of these experiences or opinions I noted above impact your decision to decline to have your research result confirmed?
- Can you tell me about your reaction to receive that call?
- What did you think about the information the genetic counselor provided?
- Can you tell me a little more about why you decide to opt out of having your research result confirmed?
    i. What were the main factors that you thought about when making that decision?
        1. What other things were going on at the time that played a role in your decision?
        2. How did the thought of how your result might impact family affect your decision?
        3. Were you worried about who would have access to this genetic test report?
            a. If yes were there specific people or organizations you were worried might gain access?
                i. Healthcare providers
                ii. Insurers (if yes to this ask them to elaborate)
                iii. Other
    ii. Did you consult with anyone when making this decision?
        1. Spouse, parent, friend, sibling, other family member?
    iii. Some individuals are able to make decisions very quickly while others take a little bit more time to come to a decision. Where would you say you fall on this spectrum? Do you remember how long it took you to make this decision about your Biobank result?
    iv. How difficult was it to decide whether or not to receive your genetic test result?

7. Can you tell me about the experience you have had with genetics and/or genomic sequencing outside of the Partners biobank project?

- Educational experiences, personal experiences, professional experiences?
- Did these experiences influence your decision about your research result?

8. Is there anything else you'd like to tell me about your experience that we haven't covered?

- Do you have any advice for others participating in a biobank?

Conclusion: Thank you so much for taking the time out of your day to complete this interview, I greatly appreciate it. We have this address on file for you, would this be the best place to send your Amazon gift card? (read address we have on file).

[If the participant expressed interest in learning their genetic testing result, or has new concerns, I will provide the contact information for the Biobank counselor who can talk about their result in more detail and discuss next steps.]

Thank you again for your time, I hope you have a great rest of your day!

If participants do not answer the phone call, the following voicemail will be left:

Hello. This message is for Mr./Mrs. (*Name).* My name is XXX and I am calling from Brigham and Women's Hospital in regard to your participation in the Partners Healthcare Biobank. Please contact me by telephone at 617-529-7738.

Thank you and have a great day. Goodbye.

*We will also interview participants who initially opted to have their result confirmed but later opted out directly or passively by not sending their saliva kit back in or not coming for their clinical appointment, after reminders from the study team.

Figure S1: Contacts Needed for Each Participant Outcome

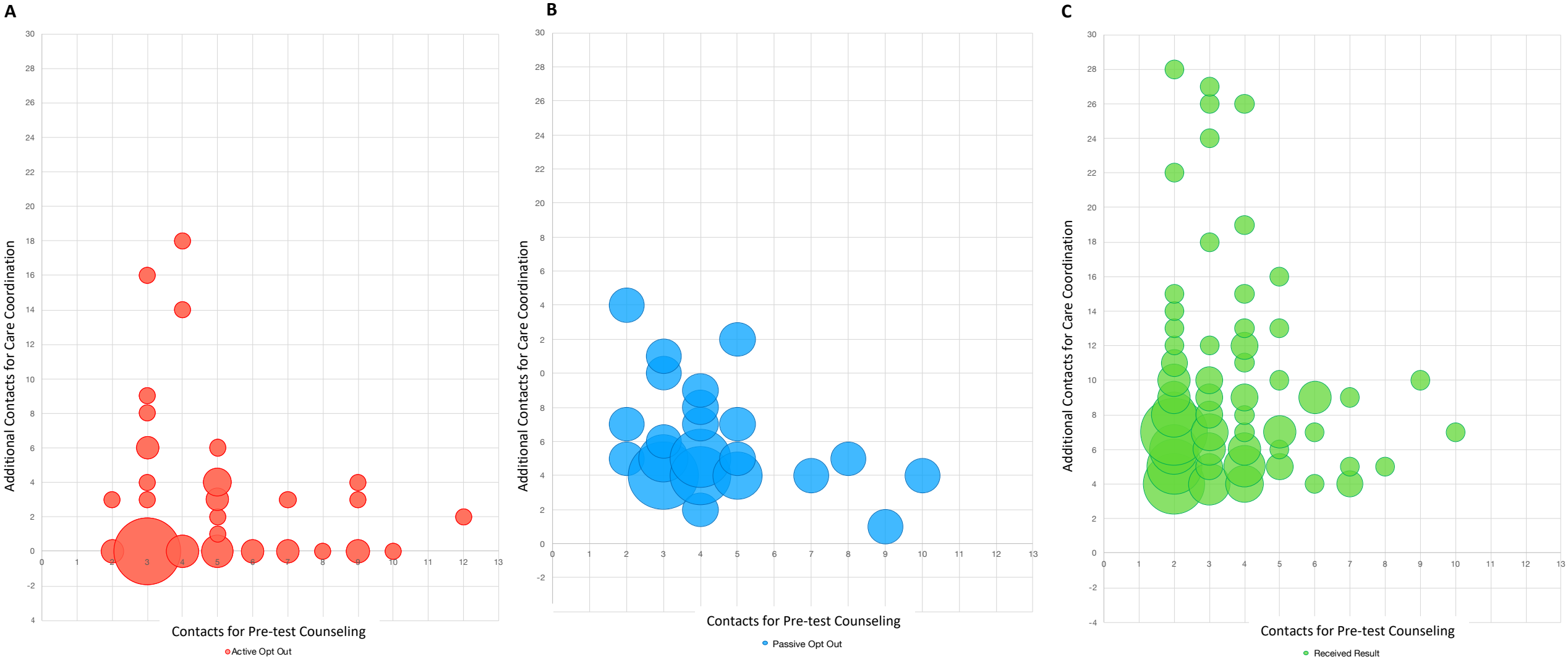

Figure S1: Panels are grouped by final outcome: participant opted out, participant passively opted out, or participant received their clinically confirmed result. Bubble sizes represent the number of contacts needed at each time point. The x axis represents the number of contacts needed to reach participants for initial notification and pre-test counseling, this included letters and phone calls, including follow-up phone calls if participants asked the study team to call them back. The y axis represents additional contacts to coordinate care after notification and counseling, this included healthcare provider, laboratory and/or patient contact by email or phone.

Figure S2: Reasons for Decline

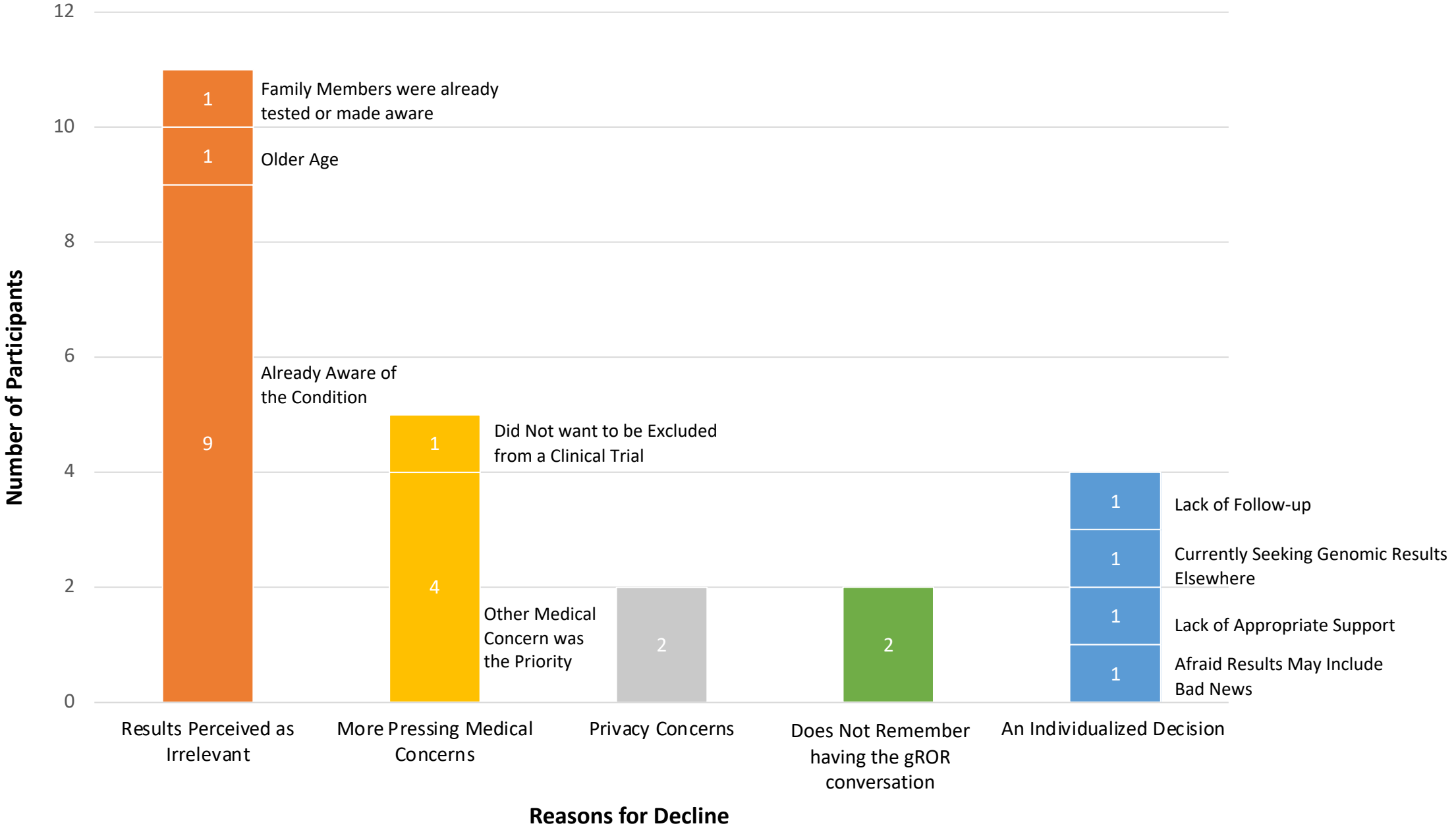

Figure S2: Reasons reported by participants for declining clinical confirmatory testing of identified genomic result

Table S1: Communication Guide

Phenotype/Associated Condition	Disease name communicated to patient	Gene	Description of disease communicated to patient
Hereditary Breast and Ovarian Cancer	Hereditary Breast and Ovarian Cancer	BRCA1	A genetic condition that causes an increased risk to develop breast, ovarian, prostate, pancreatic and other cancers.
		BRCA2	
Li-Fraumeni Syndrome	Hereditary Mixed Cancer Syndrome (different types of cancer)	TP53	A genetic condition that causes an increased risk to develop several types of cancer, particularly in children and young adults.
Peutz-Jeghers Syndrome	Hereditary Gastrointestinal Cancer Syndrome	STK11	A genetic condition that causes an increased risk to develop breast, ovarian, colorectal, gastric, and pancreatic cancers as well as noncancerous growths, called polyps, in the gastrointestinal tract (stomach and intestines).
Lynch Syndrome	Hereditary Colon Cancer Syndrome	MLH1	A genetic condition that causes an increased risk to develop many types of cancers, particularly colon cancer. In females there is also an increased risk of uterine and ovarian cancer.
		MSH2	
		MSH6	
		PMS2	
Familial Adenomatous Polyposis	Hereditary Colon Cancer Syndrome	APC	A genetic condition that causes an increased risk to develop colon cancer.
MYH-Associated Polyposis; Adenomas, multiple colorectal, FAP type 2; Colorectal adenomatous polyposis, autosomal recessive, with pilomatricomas	Hereditary Colon Cancer Syndrome	MUTYH	A genetic condition that causes an increased risk to develop colon cancer.
Juvenile Polyposis	Hereditary Gastrointestinal Polyp Syndrome	BMRP1	A genetic condition that causes an increased risk to develop cancerous and noncancerous growths, specifically in the gastrointestinal tract (stomach and intestines).
		SMAD4	
Von Hippel Lindau Syndrome	Hereditary Mixed Cancer Syndrome (different types of cancer)	VHL	A genetic condition that causes an increased risk to develop tumors and cysts in many parts of the body, including the brain, spinal cord, kidneys, and retina.
Multiple Endocrine Neoplasia Type 1	Hereditary Endocrine Cancer Syndrome	MEN1	A genetic condition that causes an increased risk to develop tumors of the endocrine (hormone-producing) glands including the parathyroid, pancreas, and pituitary gland.
Mulitple Endocrine Neoplasia Type 2	Hereditary Endocrine Cancer Syndrome	RET	A genetic condition that causes an increased risk to develop cancer and non-cancerous tumors of the thyroid and other tumors of hormonal glands.
Familial Medullary Thyroid Cancer	Hereditary Thyroid Cancer Syndrome	RET	A genetic condition that causes an increased risk to develop thyroid cancer.
PTEN Hamartoma Tumor Syndrome	Hereditary Mixed Cancer Syndrome- sometimes associated with intellectual disabilities	PTEN	A genetic condition that causes an increased risk to develop non-cancerous and cancerous tumors including the thyroid, breast, kidney and uterus. In some individuals this disorder can cause development and learning difficulties.
Retinoblastoma	Hereditary Eye Cancer Syndrome	RB1	A genetic condition that causes increased risk to develop cancer that begins in the eye (retina). There is also an increased risk of other cancers including a gland in the brain (pinealoma), bone, soft tissue, and muscle, and skin cancer.
Hereditary Paraganglioma- Pheochromcytoma Syndrome	Hereditary Paraganglioma Syndorme	SDHD	A genetic condition that causes increased risk to develop growths on hormone-producing glands that are typically non-cancerous.
		SDHAF2	
		SDHC	
		SDHB	
Tuberous Sclerosis Complex	Hereditary Syndrome that Affects the Brain, Skin and Kidneys	TSC1	A genetic condition that causes an increased risk to develop noncancerous tumors in many parts of the body, including the skin, brain, and kidneys.
		TSC2	
WT1- related Wilms tumor	Hereditary Kidney Cancer Syndrome	WT1	A genetic condition that causes an increased risk to develop kidney tumors in childhood.
Neurofibromatosis type 2	Hereditary Nervous System Benign Tumor Syndrome	NF2	A genetic condition that causes an increased risk to develop non-cancerous tumors of the nerves , sometimes causing hearing loss.

Ehlers-Danlos Syndrome- vascular type	Hereditary Connective Tissue Disorder That Can Cause Aortic Dilataion	COL3A1	A genetic condition that causes an increased risk to develop dilated (enlarged) blood vessels, and rupture of the uterus, intestine and aorta.
Marfan Syndrome, Loeys-Dietz Syndromes, and Familial Thoracic Aortic Aneurysms and Dissections	Hereditary Connective Tissue Disorder That Can Cause Aortic Dilataion	FBN1	A genetic condition that causes an increased risk to develop dilated (enlarged) blood vessels, and rupture of the uterus, intestine and aorta.
		TGFBR1	
		TGFBR2	
		SMAD3	
		ACTA2	
		MYH11	
Fabry Disease	Hereditary Disorder That Affects The Heart, Kidneys And Some Other Organs	GLA	A genetic condition that causes an increased risk to develop kidney failure, strokes, heart disease, and other medical issues.
Hypertrophic cardiomyopathy, Dilated cardiomyopathy	Hereditary Cardiomyopathy (Enlarged Heart)	MYBPC3	A genetic condition that causes an increased risk to develop a heart problem called cardiomyopathy. This can cause heart failure or an abnormal heart rhythm that can cause the heart to stop beating.
	Hereditary Cardiomyopathy (Enlarged Heart)	MYH7	
	Hereditary Cardiomyopathy (Enlarged Heart)	TNNT2	
	Hereditary Cardiomyopathy (Enlarged Heart)	TNNI3	
	Hereditary Cardiomyopathy (Enlarged Heart)	TPM1	
	Hereditary Cardiomyopathy (Enlarged Heart)	MYL3	
	Hereditary Cardiomyopathy (Enlarged Heart)	ACTC1	
	Hereditary Cardiomyopathy (Enlarged Heart)	PRKAG2	
	Hereditary Cardiomyopathy (Enlarged Heart)	MYL2	
	Hereditary Cardiomyopathy (Enlarged Heart)	LMNA	
Catecholaminergic polymorphic ventricular tracycardia	Hereditary Heart Rhythm Disorder	RYR2	A genetic condition that causes an increased risk to develop an abnormal heart rhythm (arrhythmia) that can cause the heart to stop beating.
Arrythmogenic right ventricular cadriomyopathy	Hereditary Heart Rhythm Disorder	PKP2	A genetic condition that causes an increased risk for developing heart problems, such as heart failure or an abnormal heart rhythm that can cause the heart to stop beating.
		DSP	
		DSC2	
		TMEM43	
		DSG2	
Romano-Ward Long QT Syndromes Types 1,2, and 3, Brugada Syndrome	Hereditary Heart Rhythm Disorder	KCNQ1	A genetic condition that causes an increased risk to develop an abnormal heart rhythm (arrhythmia) that can cause the heart to stop beating.
		KCNH2	
		SCN5A	
Familial hypercholesterolemia	Hereditary High Cholesterol Disorder	LDLR	A genetic condition that can cause increased risk to develop high cholesterol levels which can cause problems with the heart and blood vessels. In some people this can be much more significant than typical high cholesterol that many people have.
		APOB	
		PCSK9	
Wilson Disease	Hereditary Copper Metabolism Disorder	ATP7B	A genetic condition that can cause increased risk for copper to build up in the organs which can cause liver failure, mental health issues and abnormal muscle movements.
Orinthine transcarbamylase deficiency	Hereditary Urea Cycle Disorder	OTC	A genetic condition that increases the risk for ammonia to accumulate in the blood. This can cause neurological problems including learning issues, confusion and life-threatening comas.
Malignant hyperthermia susceptibility	Hereditary Disorder- Causing Abnormal Response to Anesthesia	RYR1	A genetic condition that increases the risk to develop severe reactions to certain drugs used for general anesthesia.

Laboratory Methods

Genotyping arrays: Genotyping of 36,417 MGB Biobank samples utilized one of three versions of the Illumina (San Diego, CA) Infinium Multi-Ethnic Genotyping arrays that were developed to capture both variation among a diversity of genetic backgrounds and functional variation within the genome. The three versions included: 1) a pre-release version developed by the Multi-Ethnic Genotyping Array Consortium (MEGA), 2) an expanded version of the pre-commercial Expanded Multi-Ethnic Genotyping Array (MEGAEX), and 3) the final commercial version of the Multi-Ethnic Global (MEG). A substantial number of probes from MEGA and MEG were re-designed in later versions due to quality and probe re-synthesis issues. Therefore, for both pre-commercial arrays the analyzed probes were limited to the content of the final MEG array. Additionally, for each array the probe coordinates were remapped based on the TopGenomicSeq in the manifest provided by Illumina to more accurately determine probe location for downstream annotations.

Sample Processing: The initial 4924 samples assayed using the MEGA array were genotyped at Illumina, while genotyping using the MEGAEX and MEG arrays were conducted internally at the MGB Biobank Genomics Core. For all samples, quantification to assess the concentration of double-stranded DNA was conducted using picogreen, and 200-400 ng of genomic DNA was amplified using a whole genome amplification process. Genotyping was then performed following the same procedures using the Illumina-recommended protocol. Quality control (QC) of the genotyping arrays was carried out by looking at the Controls Dashboard within Genome

Studio. These controls monitor internal spike in probes at various points of the process and allow the QC of sample dependent and sample independent processes.

Genotyping processing: For analysis, batch sizes targeting 5,000 subjects were created to enable quicker return of actionable results rather than waiting for all genotypes to be generated. For each batch of data, the GTC files generated in Illumina LIMS were converted to PED file format using a customized script based on Illumina provided code that tracks array annotations and specimen annotations. During this conversion from GTC files to PED, pre-defined probes that underperformed (<95% call rate) or were not able to be mapped to GRCh37 were removed.[1] All samples required an overall call rate >99% as calculated by Illumina LIMS using a cluster file specific for each array version. Data for subjects in which a gender mismatch was identified and not resolved or data for a participant that had subsequently withdrawn from the study were removed from analysis. The datasets for the remaining subjects were converted to individual vcf files.

Genomic sequencing: A subset of 2349 genotyped individuals were sequenced for a limited set of genes as part of the Electronic Medical Records and Genomics (eMERGE) III program.[2] Further, a set of 914 additional individuals who self-reported as Hispanic or Latino, Black or African American or other in the MGB EHR were prioritized for analysis from exome sequencing data. Briefly, exome sequencing was run at the Broad Institute of Harvard and MIT using a custom capture library from TWIST Biosciences (approximately 37Mb target) with sequencing on the Illumina NovaSeq using 150 bp paired reads. The hybrid selection libraries met or

exceeded 85% completeness of exonic targets at 20x, which is comparable to approximately 55x mean coverage. Exome sequences were aligned to GRCh38, joint-called using the Genome Analysis ToolKit (GATK) across the biobank cohort, and converted back to GRCh37 coordinates for interpretation.

Data and Code Availability: Individual-level data are available from the Mass General Brigham Biobank; however, there are restrictions on this data which was accessed under IRB protocol 2009P002312 for this current study, so some data are not publicly available. Samples sequenced or genotyped as part of the eMERGE consortium are deposited in dbGAP https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001616.v1.p1 and https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001584.v2.p2.

Supplemental References:

1. Blau, A., Brown, A., Mahanta, L., and Amr, S.S. (2016). The Translational Genomics Core at Partners Personalized Medicine: Facilitating the Transition of Research towards Personalized Medicine. J Pers Med 6.
2. eMERGE Consortium. (2019). Harmonizing clinical sequencing and interpretation for the eMERGE III Network. American journal of human genetics 105, 588-605.