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]

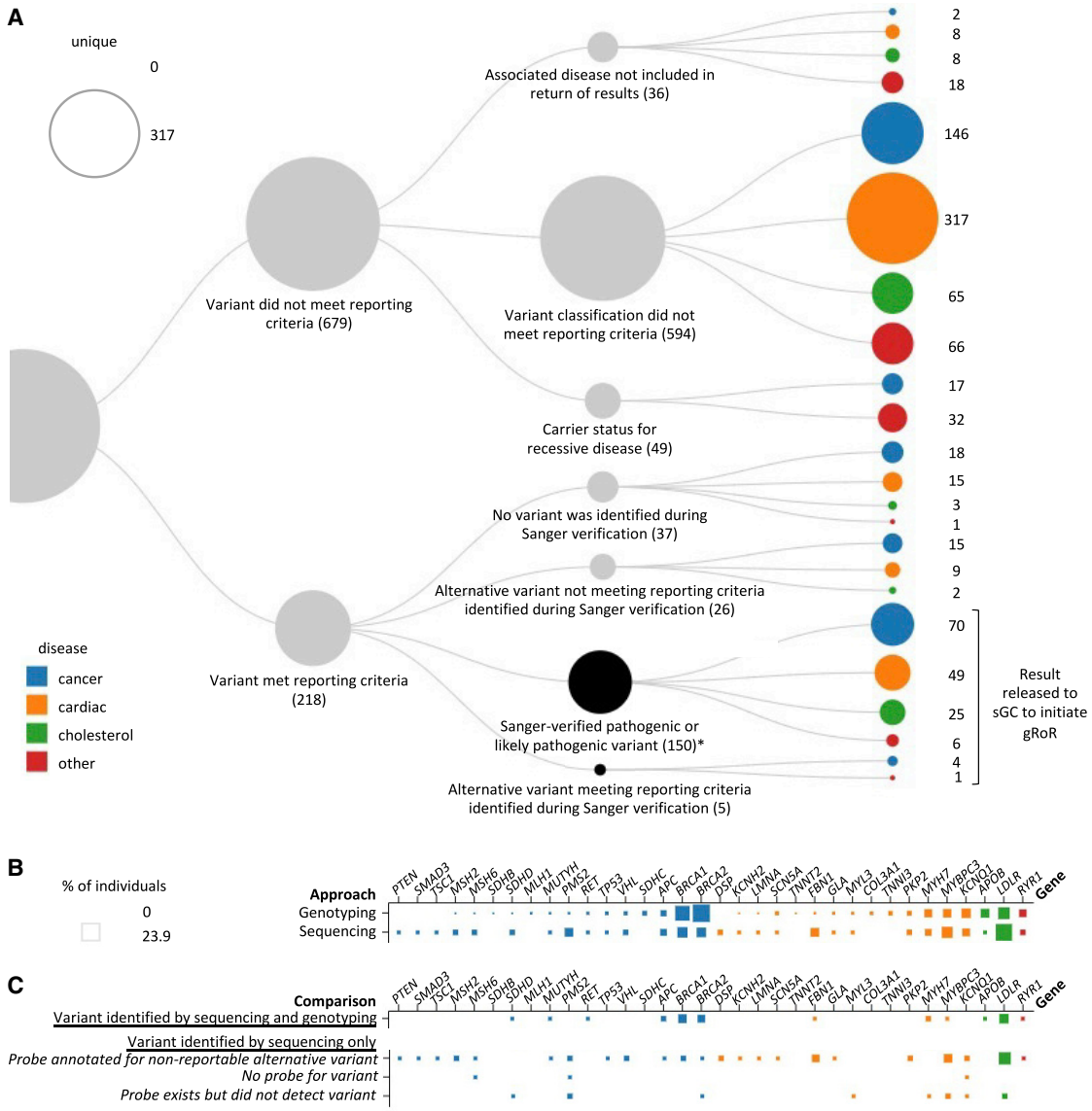

Figure 1. Interpretation of research data and yield per platform, disease area, and gene

(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

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

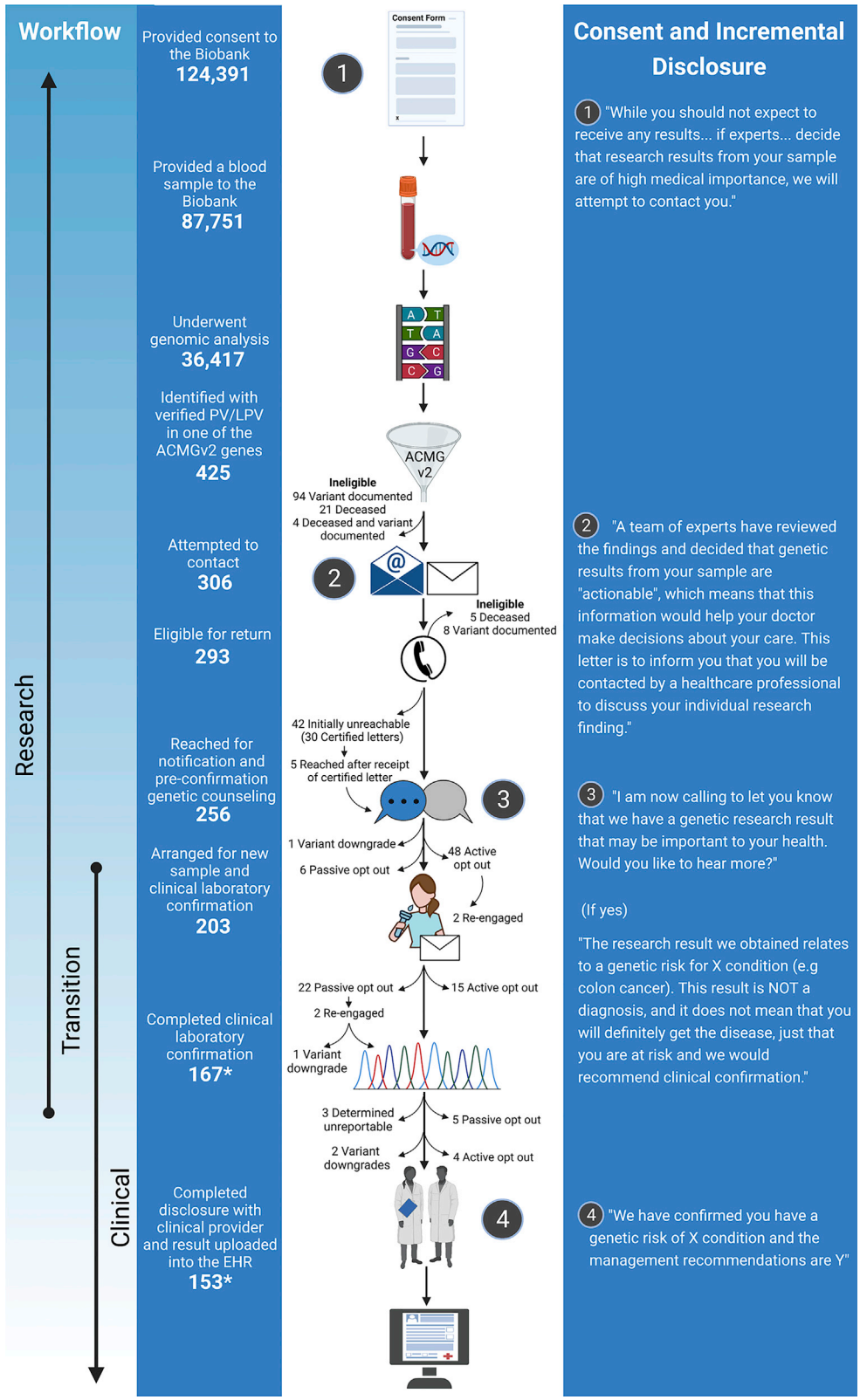

Figure 2. Participant flow through the biobank incremental disclosure gRoR process
Asterisks indicate that this number includes ten participants that have elected to proceed with gRoR and are in progress but have not completed it.

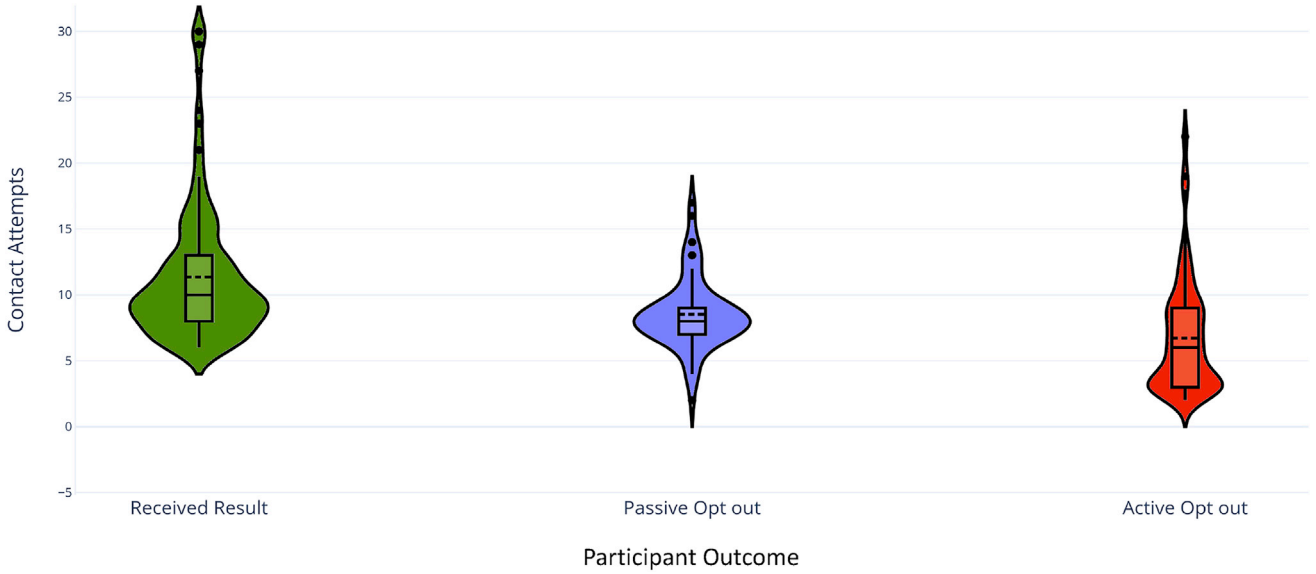

Figure 3. Number of contacts and contact attempts needed for each participant outcome
Participants are grouped into three kernel density plots that show the range of contact attempts needed to successfully disclose a result to participants (green) or to reach active (red) or passive (purple) opt out 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).

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

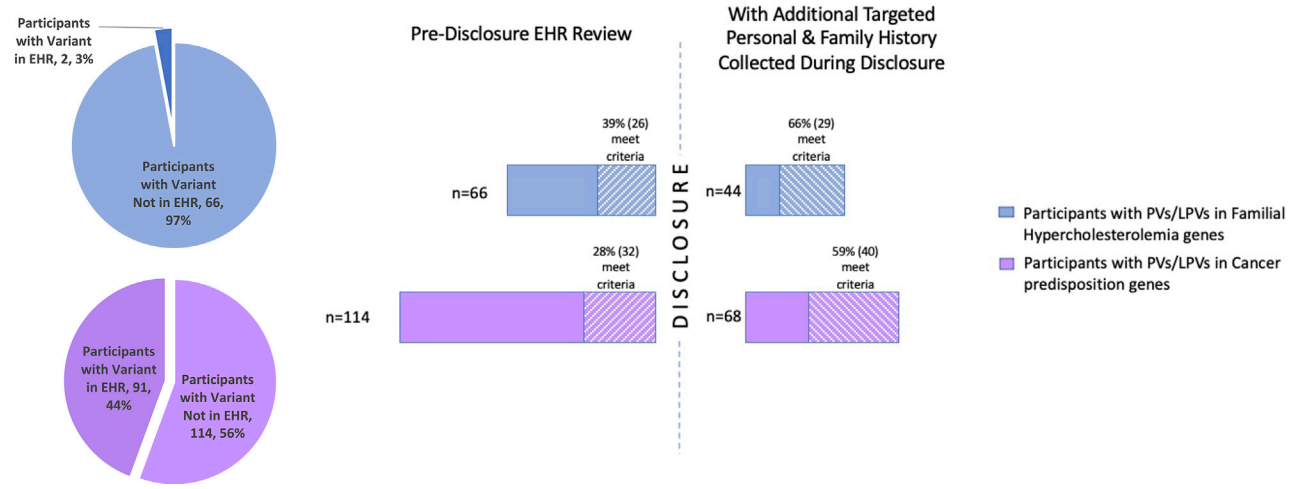

Figure 4. Electronic health record (EHR) review of those meeting professional guideline criteria for clinical genetic testing
EHRs were reviewed for participants with PLPVs in three familial hypercholesterolemia (FH, blue) genes and 22 cancer predisposition genes (purple). Pie charts reveal the percentage 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

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

BioRender, https://biorender.com/

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