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Clinical Implementation of Combined Monogenic and Polygenic Risk Disclosure for Coronary Artery Disease

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Abstract

BACKGROUND—State-of-the-art genetic risk interpretation for a common complex disease such as coronary artery disease (CAD) requires assessment for both monogenic variants—such as those related to familial hypercholesterolemia—as well as the cumulative impact of many common variants, as quantified by a polygenic score.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.

OBJECTIVES—The objective of the study was to describe a combined monogenic and polygenic CAD risk assessment program and examine its impact on patient understanding and changes to clinical management.

METHODS—Study participants attended an initial visit in a preventive genomics clinic and a disclosure visit to discuss results and recommendations, primarily via telemedicine. Digital postdisclosure surveys and chart review evaluated the impact of disclosure.

RESULTS—There were 60 participants (mean age 51 years, 37% women, 72% with no known CAD), including 30 (50%) referred by their cardiologists and 30 (50%) self-referred. Two (3%) participants had a monogenic variant pathogenic for familial hypercholesterolemia, and 19 (32%) had a high polygenic score in the top quintile of the population distribution. In a postdisclosure survey, both the genetic test report (in 80% of participants) and the discussion with the clinician (in 89% of participants) were ranked as very or extremely helpful in understanding the result. Of the 42 participants without CAD, 17 or 40% had a change in management, including statin initiation, statin intensification, or coronary imaging.

CONCLUSIONS—Combined monogenic and polygenic assessments for CAD risk provided by preventive genomics clinics are beneficial for patients and result in changes in management in a significant portion of patients.

Keywords

coronary artery disease; genetics; genomic medicine; polygenic score; precision medicine; preventive cardiology

Despite guideline-directed clinical risk calculators and preventive treatments, coronary artery disease (CAD) remains the leading cause of mortality, highlighting a need for earlier and better identification of people at risk.[1,2] Clinical risk calculators such as the American College of Cardiology/American Heart Association Pooled Cohort Equations (PCE) estimate 10-year atherosclerotic cardiovascular disease (ASCVD) risk to guide patient risk discussion around initiating statin therapy to lower low-density lipoprotein cholesterol (LDL-C).[3] However, the PCE and other tools are validated for use in patients aged at least 40 years or are dependent on the presence of clinical risk factors such as high blood pressure or diabetes mellitus.[2] As CAD is a heritable disease[4] and DNA is known from the time of birth, there is an opportunity to use genetic information to improve the identification of people at risk of CAD.

Genetic information augments our ability to identify people at high risk of CAD in at least 3 ways, but it remains challenging to integrate into clinical practice. First, a “genome-first” approach can help stratify risk before the onset of clinical risk factors. Second, clinical risk and genetic risk are additive, and considering both provides the strongest risk prediction even in middle age.[5,6] Third, individuals with high genetic risk derive greater relative and absolute protection from CAD from lipid-lowering therapies based on post hoc analyses of completed trials.[7–9] Despite those potential benefits, returning genetic risk information to individuals in a preventive genomics framework requires more research to understand how risk is best communicated and its impact on clinical care and motivation for a lifestyle change.

State-of-the-art interpretation of genetic risk for a common complex disease such as CAD requires reporting combined monogenic and polygenic assessments.[10] Monogenic variants pathogenic for familial hypercholesterolemia are relevant to ~0.4% of the population who are at about a 3-fold increased risk of CAD,[11,12] yet they remain underdiagnosed and undertreated in contemporary practice.[13,14] Reporting monogenic risk results is well understood with existing guidelines and criteria,[15] testing is currently performed clinically for patients with high LDL-C and family history,[16] and familial hypercholesterolemia has been classified by the Center for Disease Control and Prevention as a tier 1 condition with potential for positive impact on public health.[17] In contrast, a polygenic score for CAD is a quantitative measure of risk integrating the cumulative effect of many variants across the genome.[18] Polygenic score stratifies risk in everyone in the population across a gradient, with individuals with high polygenic scores having an increased risk of CAD, sometimes equivalent to or higher than familial hypercholesterolemia.[11,18] Unlike monogenic risk, optimal reporting of a polygenic score is more complex and is a recognized major gap that is recently being studied by our group and a few others.[19–23]

Our study sought to build on prior studies in at least 3 ways. First, no prior studies explored the combined monogenic and polygenic risk assessment of CAD in the context of a real-world preventive genomics clinic. Second, prior studies used older polygenic scores with a limited number of single nucleotide polymorphisms.[19] In the present study, we use a more recent genome-wide polygenic score, which has improved power compared with older scores.[10–12] Third, we describe a framework for reporting that promotes the understanding of risk results by both integrating it in a clinical visit and using reporting and educational tools that have been optimized through user experience testing.[20] In the context of this clinic structure, we examined the impact of the combined monogenic and polygenic CAD risk assessment on patient understanding and changes in clinical management.

METHODS

PARTICIPANTS.

Participants were recruited from adult individuals who self-referred or were referred by a physician for genetic testing of CAD at the Massachusetts General Hospital Preventive Genomics Clinic. Visits occurred virtually or in person, the clinical genetic test was offered free of charge, and participants were seen by a medical doctor and/or a genetic counselor and completed surveys at enrollment and 1 follow-up visit (Supplemental Figure 1).

The study was approved by the Mass General Brigham Institutional Review Board (protocol number 2020P003088), and all participants provided consent to participate.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

GENETIC TESTING.

Participants provided their saliva samples at the clinic or remotely through a ship-to-home kit. Participants received low-coverage whole genome sequencing and a multigene next-generation sequencing panel test from Color Health, Inc ("Color," Burlingame, CA) under Clinical Laboratory Improvements Amendments (#05D2081492) and College of American Pathologists (#8975161) compliance.[24,25] Monogenic test results for CAD were obtained by evaluating the presence of pathogenic or likely pathogenic variants in 3 familial hypercholesterolemia–related genes, *LDLR*, *APOB*, and *PCSK9*, from a broader monogenic testing panel. Variants were classified according to the American College of Medical Genetics and Genomics 2015 guidelines for sequence variant interpretation and signed out by a board-certified medical geneticist or pathologist.[26]

Polygenic score calculation was performed using a previously published score of CAD consisting of 6.6 million variants.[11,24] To perform ancestry-based score normalization on the low-coverage whole genome sequencing data, Locating Ancestry from SEquence Reads was used to project the individual's genetic data on a built-in ancestry reference panel of approximately 4,000 ethnically diverse samples. Then, a principal component–based linear model was constructed using a cohort of ~25,000 nonrelated individuals from the Color research database. The standardized residual of the score was used to calculate the normalized score, following correction for the first 10 principal components. Finally, the distribution of the score was verified to have a mean of approximately zero and a standard deviation of one, ensuring a normalized distribution. The results were reported as a percentile, 0th to 99th, each with increasing relative risk compared with the general population.[20]

RETURN OF RESULTS.

The results were returned virtually or in person during a follow-up visit with a cardiologist and/or a genetic counselor. During this visit, the clinicians disclosed the results of the test, discussed potential downstream implications, and documented the results in the electronic medical record. Participants were then sent a monogenic test result report from the genetic testing company, a dedicated polygenic score report for CAD,[20] and a link to a polygenic score explainer website (http://polygenicscores.org/) via Patient Gateway, the hospital's secure patient communication portal.

SURVEYS.

All participants were asked to complete 2 surveys—one at the time of enrollment (baseline survey—Supplemental Table 1) and another made available digitally following the return of results (postdisclosure survey—Supplemental Table 2). The baseline survey assessed the participant's demographics, lifestyle, and dietary behaviors. The postdisclosure survey assessed the participant's understanding of genetic test results according to the different resources provided, their perceived anxiety level as per the 6-item short-form of the Spielberg State-Trait Anxiety Inventory,[27] and their intent to change their lifestyle and dietary behavior.

STUDY OUTCOMES.

At enrollment, electronic medical records were reviewed to collect data on the participant's relevant medical history, vital signs, laboratory values, imaging, and medication list. At follow-up, records were reviewed to document changes in clinical management following the return of results. Study outcomes included participants' understanding of the genetic test results, participants' intent to adopt a healthier lifestyle, and change in clinical management by the treating clinician, which included initiation or intensification of statin therapy or coronary imaging scan.

STATISTICAL ANALYSIS.

Statistical analysis was carried out using R software version 4.1.0 (R Foundation for Statistical Computing). Statistics were presented as proportions for categorical variables and as mean ± SD or median (IQR) for continuous variables. Findings were compared by sex, age group, referral pathway, CAD status, and responder status to postdisclosure survey. A chi-square test of independence or a Fisher exact test was used for categorical variables, and an unpaired *t*-test was used for continuous variables, with the level of statistical significance set at $P < 0.050$.

RESULTS

STUDY PARTICIPANTS.

We enrolled 60 participants (mean age 50.8 years, 37% women, 70% of European ancestry) between December 2020 and August 2021 (Table 1, Supplemental Figure 1). There were 30 self-referred participants and 31 referred by a cardiologist, one of whom withdrew from the study, resulting in a total of 60 participants (Supplemental Table 3). Most clinic visits (93% of initial and 100% of disclosure visits) were performed virtually. Study participants were of higher socioeconomic status—65% reported more than $140,000 U.S. dollars in annual household income and 65% had graduate or professional degrees (Table 1). Most participants had no known history of CAD and were looking for a better evaluation of their risk because of strong family history or presence of clinical risk factors, but 28% of participants had a known diagnosis of CAD and enrolled with the hope of explaining their increased risk. As such, the study cohort was enriched for clinical CAD risk factors compared with the general population—67% with a first-degree relative with CAD or ischemic stroke, 60% with a history of hyperlipidemia, 18% with hypertension, and 5% with diabetes mellitus (Table 1).

The baseline survey was completed by 52 participants after a median duration of 1 day after the initial visit, and the postdisclosure survey was completed by 30 participants within a median of 18 days from receiving genetic testing results (Supplemental Figure 1). The participants had a healthy lifestyle at baseline without significant differences by referral pathway (Supplemental Table 4). For example, 86% met the exercise recommendations of the Physical Activity Guidelines for Americans,[28] and 33% reported eating at least 2.5 servings of vegetables and 2 servings of fruits daily, as recommended by the 2015 to 2020 Dietary Guidelines for Americans (Table 1).[29]

CLINICAL MONOGENIC AND POLYGENIC TEST RESULTS.

Combined monogenic and polygenic testing results were returned to 59 participants during the disclosure visit (Supplemental Figure 1). One participant received only monogenic test results due to sample failure. Two participants (3%) had a familial hypercholesterolemia variant, both of which were pathogenic variants in *LDLR*—c.820del (p.Thr274Hisfs*96) and c.1216C>A (p.Arg406=) (Figure 1A). The 2 familial hypercholesterolemia variant carriers were also found to have high polygenic scores, defined as being in the top quintile of the population distribution (Figure 1B).

Participant polygenic scores ranged from the 2nd to the 99th percentile (Supplemental Tables 5 and 6). The mean polygenic score percentile was higher in participants with CAD compared with those without CAD (76 vs 59; $P = 0.044$). In addition to the 2 monogenic carriers who also had a high polygenic score, 19 (32%) of participants had a high polygenic score, 30 (51%) had an intermediate score, defined as being in the middle 3 quintiles of the population distribution, and 8 (14%) had a low polygenic score, defined as being in the lowest quintile (Figure 1A). The mean polygenic score percentile did not differ between participants referred by a cardiologist and those who self-referred (70 vs 58, $P = 0.119$).

POSTDISCLOSURE UNDERSTANDING, FEELINGS, AND MOTIVATION FOR A LIFESTYLE CHANGE.

Thirty-six participants completed a digital postdisclosure survey and provided data for their understanding of the genetic test results based on the different resources available. The average polygenic score percentile did not differ between those who filled the postdisclosure survey and those who did not (61 vs 71; $P = 0.211$). Most participants found the various resources such as polygenic score report, explainer website, and virtual visit with a clinician "very" or "extremely" helpful to better understand their results (Table 2). Thirty-five (97%) described learning something valuable about their health.

The postdisclosure survey also assessed participants' feelings through a rating of specific feelings statements. Most participants expressed a "moderate" or "very much" agreement with "I feel content" (83%), "I feel calm" (78%), and "I feel relaxed" (69%). Conversely, only 2 (6%) participants expressed a "moderate" or "very much agreement" with "I feel worried", 2 (6%) expressed a "moderate" or "very much" agreement with "I feel tense", and 1 (3%) participant expressed a "moderate" or "very much" agreement with "I feel upset".

With genetic risk communication and understanding, it is important that people develop motivation and intent to make positive lifestyle changes to reduce their risk. Among participants with a suboptimal diet at baseline (n = 25)—defined as lower than the recommended daily servings of fruits and vegetables[29]—17 (68%) participants expressed intent to improve their diet. Three participants had suboptimal physical activity at baseline—defined as <150 minutes of moderate-intensity exercise per week, <75 minutes of vigorous-intensity exercise per week, or an equivalent combination of both[2]—and all of them expressed intent to exercise more frequently after receiving the result (Table 3, Supplemental Table 7).

CHANGE IN MANAGEMENT AMONG PARTICIPANTS WITHOUT CAD.

Despite the lack of clinical guidelines to initiate diagnostic or therapeutic interventions for CAD based on polygenic scores, physicians used the genetic test as an additional risk assessment tool in conjunction with clinical risk factors to guide additional interventions. Nearly half of participants without CAD (17 of 42 patients or 40%) had a change in management that fell into 2 categories (Central Illustration). First, there were changes in pharmacotherapy, including the prescription or intensification of lipid-lowering medications to prevent or delay CAD development. Second, there were diagnostic coronary imaging scans to assess for existing coronary plaque or measure a coronary calcium score, both of which can potentially incentivize the initiation or intensification of lipid-lowering medications (Figure 2, Supplemental Tables 8 and 9).[2,3]

Twenty-six participants did not have CAD and were not on a lipid-lowering medication at enrollment. Following genetic test results disclosure, 10 (38%) of them were prescribed a statin with the goal of lowering LDL-C levels and preventing or delaying the onset of CAD (Figure 2, Supplemental Table 8). All 10 of those participants had LDL-C levels above 100 mg/dL and had at least 1 additional risk factor for CAD, including a body mass index above 25 kg/m^2 (n = 9), a first-degree relative with ASCVD (n = 8), hyperlipidemia managed with lifestyle modifications only (n = 5), a history of cigarette smoking (n = 2), and hypertension (n = 1). Notably in those participants, the PCE 10-year estimated ASCVD risk alone would not have resulted in recommending a statin prescription. Only 2 of the 10 participants had a PCE 10-year estimated ASCVD risk ≥5%, a guideline-accepted threshold for shared decision-making around the initiation of statin.[2] The remaining were either below that threshold (n = 5) or their 10-year ASCVD risk could not be estimated (n = 3) because they were younger than the age cutoff for which the calculator is validated for use.[2]

Another 10 participants without CAD were already on a low- or moderate-intensity statin at enrollment. Of those, 2 (20%) had their statin dose intensified to a high-intensity statin to achieve lower LDL-C (Figure 2, Supplemental Table 8). Finally, there were no participants without CAD on a statin with a low polygenic score, and as such, de-escalation of statin therapy was not seen.

As for recommendations for coronary imaging scans among 32 eligible participants without diagnosed CAD and without any coronary imaging scan within the last 5 years, 6 (19%) had a coronary imaging scan recommended following the return of results via a personalized approach (Figure 2, Supplemental Tables 8 and 10).

Changes in clinical management occurred more frequently in younger participants—7 of 10 (70%) in the 20 to 39 years age group, 9 of 23 (39%) in the 40 to 59 years age group, and 1 of 9 (11.1%) in the >60 years age group ($P = 0.032$). There were no differences by sex or referral pathway (Supplemental Table 11).

RETURN OF GENETIC TEST RESULTS TO PARTICIPANTS WITH KNOWN CAD.

Seventeen (28%) participants had known CAD at enrollment, were followed by a cardiologist, and had their cardiovascular risk factors optimized. As such, there were no changes in management following the return of results. Among participants with CAD and a

high polygenic score, 8 (80%) had discussions with the clinician around the consideration of genetic testing for their first-degree relatives with no diagnosed CAD. Furthermore, 8 (89%) of those with CAD who completed the postdisclosure survey reported that they learned valuable information after disclosure of genetic test results.

DISCUSSION

In this study, we described the return of a combined monogenic and polygenic risk result for CAD as part of a clinical assessment in a preventive genomics clinic and examined its impact on the understanding of genetic test results, intent for a healthy lifestyle, and change in clinical management. This comprehensive test identified 35% of participants as being at high genetic risk for CAD, defined as having a pathogenic familial hypercholesterolemia variant, or a polygenic score in the top quintile of the general population distribution for polygenic scores (Central Illustration). The test also identified 3% of the participants who were predisposed to CAD because of both a pathogenic familial hypercholesterolemia variant and a high polygenic score. Identifying individuals at high genetic risk, particularly early in life and before the onset of clinical risk factors, is a major potential benefit of genetic risk assessment.[18] Few prior studies have focused on the implementation of such a strategy in the context of a preventive genomic framework,[19,30] especially using a combined monogenic and polygenic assessment.[31] Large-scale efforts for polygenic score implementation are underway by groups such as the eMERGE Network of investigators and Our Future Health.[32,33]

Understanding genetic risk and subsequently associating one's risk with an intent to make positive lifestyle changes is an important first step that needs to be achieved with reporting.[23] We provided one generalizable framework of how results could be disclosed in a way that enhances understanding by focusing on the use of rich educational and reporting tools and coupling the disclosure of results with a telemedicine visit that allows for questions and answers. Participants found the resources provided in this study helpful in enhancing their understanding of their genetic risk. Increased intent to make positive lifestyle changes was also seen in this study following the disclosure of the combined genetic test result. It is not clear that the return of genetic high-risk results is always motivating for individuals to make lifestyle changes.[34] For example, it is conceivable that individuals might interpret results negatively as being destined to have high risk. In our study, most participants (69%) expressed feeling content, relaxed, or calm, and only 3 participants (8%) expressed feeling worried, tense, or upset. Although observations in this uncontrolled study are limited by selecting participants who are already motivated to understand their risk and as such act positively on it, the findings are reassuring for the intent to pursue a healthier lifestyle and the absence of unintended effects such as fear arousal, consistent with prior studies.[34,35] More studies are needed to better understand the impact of the combined monogenic and polygenic risk assessment on participant lifestyle change through a randomized approach, a more diverse study sample, and prospective follow-up to identify whether participants act on their intent. The learnings from this study however suggest that coupling the result with rich education through a clinical visit, which includes counseling, an educational polygenic score report, and companion tools, such as our polygenic score explainer website is one approach that might enhance positive behavior change after returning a high-risk result. We

also showed that the experience could be delivered entirely virtually through telemedicine, at-home genetic testing kits, and digital communication, as was the case for 57 (95%) of our study participants.

Among participants with no known diagnosis of CAD, there was a notable change in management aimed at primary prevention and the assessment of subclinical CAD following the disclosure of the genetic risk results. Nearly half of participants with no existing CAD were recommended to initiate a statin, intensify statin therapy, or pursue additional coronary imaging scans to potentially incentivize statin initiation (Central Illustration). Our study illustrated a high tendency to prescribe statin therapy to prevent or delay the onset of CAD upon return of high polygenic score result, consistent with prior studies.[19,30] The vast majority of those who had a change in statin prescription would not have been detected by a clinical risk calculator alone. This is consistent with prior data from our group and others showing that current guidelines are limited in identifying people at risk and polygenic scores for CAD can improve the performance of clinical risk calculators.[6,36,37] Given this opportunity for a clinical utility of combined monogenic and polygenic risk assessment, future studies could use a similar implementation framework to design protocols to prospectively study individuals who do not meet clinical criteria of risk.

STUDY LIMITATIONS.

First, participants are from a high educational and economic background and are therefore more likely to reflect a subtype of the general population that is highly engaged in preventive medicine. Second, although more than a quarter of participants identified as South or East/Southeast Asian, our cohort lacked diversity in other underrepresented minority populations. There is a need to further explore the utility of this combined genetic test and the implications of returning results in larger and more diverse populations. Third, although participants were asked to fill the baseline and postdisclosure surveys immediately after the clinic visits because of the virtual nature of clinic visits and the online delivery of surveys, there were missing surveys, and surveys completed at variable times after a visit. This increases the potential for recall bias in this study and highlights a limitation of telemedicine-based research as virtual interactions are likely to have lower engagement than in-person visits.

CONCLUSIONS

We provide a generalizable framework for combined monogenic and polygenic risk disclosure in a clinical setting that could inform future clinical implementation and research. With continued evidence emerging on the role of polygenic scores in improving risk interpretation for a common complex disease such as CAD, implementation models are critical in helping to understand clinical utility. In the context of CAD, our results suggest that combined testing of monogenic and polygenic drivers as part of a clinical visit is feasible and understandable to people. Testing also identified individuals who may benefit from preventive therapies or additional diagnostic testing resulting in a change in clinical management in participants at high inherited risk, especially when other clinical assessment tools failed to highlight their increased risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ASCVD	atherosclerotic cardiovascular disease
CAD	coronary artery disease
LDL-C	low-density lipoprotein cholesterol
PCE	pooled cohort equations

REFERENCES

1. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. Int J Cardiol. 2013;168(2):934–945. 10.1016/j.ijcard.2012.10.046 [PubMed: 23218570]
2. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;74(10):e177–e232. [PubMed: 30894318]
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;73(24):3168–3209. 10.1016/j.jacc.2018.11.002 [PubMed: 30423391]
4. Khera AV, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. Nat Rev Genet. 2017;18(6):331–344. 10.1038/nrg.2016.160 [PubMed: 28286336]

5. Inouye M, Abraham G, Nelson CP, et al. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. J Am Coll Cardiol. 2018;72(16):1883–1893. 10.1016/j.jacc.2018.07.079 [PubMed: 30309464]
6. Hindy G, Aragam KG, Ng K, et al. Genome-wide polygenic score, clinical risk factors, and long-term trajectories of coronary artery disease. Arterioscler Thromb Vasc Biol. 2020;40(11):2738–2746. 10.1161/ATVBAHA.120.314856 [PubMed: 32957805]
7. Natarajan P, Young R, Stitziel NO, et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. Circulation. 2017;135(22):2091–2101. 10.1161/CIRCULATIONAHA.116.024436 [PubMed: 28223407]
8. Mega JL, Stitziel NO, Smith JG, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. Lancet. 2015;385(9984):2264–2271. 10.1016/S0140-6736(14)61730-X [PubMed: 25748612]
9. Marston NA, Kamanu FK, Nordio F, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score: results from the FOURIER trial. Circulation. 2020;141(8):616–623. 10.1161/CIRCULATIONAHA.119.043805 [PubMed: 31707849]
10. Fahed AC, Wang M, Homburger JR, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. Nat Commun. 2020;11(1):3635. 10.1038/s41467-020-17374-3 [PubMed: 32820175]
11. Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50(9):1219–1224. 10.1038/s41588-018-0183-z [PubMed: 30104762]
12. Khera AV, Chaffin M, Zekavat SM, et al. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. Circulation. 2019;139(13):1593–1602. 10.1161/CIRCULATIONAHA.118.035658 [PubMed: 30586733]
13. Patel AP, Wang M, Fahed AC, et al. Association of rare pathogenic DNA variants for familial hypercholesterolemia, hereditary breast and ovarian cancer syndrome, and Lynch syndrome with disease risk in adults according to family history. JAMA Netw Open. 2020;3(4):e203959. 10.1001/jamanetworkopen.2020.3959 [PubMed: 32347951]
14. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478–3490. 10.1093/eurheartj/eht273 [PubMed: 23956253]
15. Matthijs G, Souche E, Alders M, et al. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet. 2016;24(1):2–5. 10.1038/ejhg.2015.226 [PubMed: 26508566]
16. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia. J Am Coll Cardiol. 2018;72(6):662–680. 10.1016/j.jacc.2018.05.044 [PubMed: 30071997]
17. Tier 1 genomics applications and their importance to public health | CDC. Accessed December 16, 2021. https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm
18. Aragam KG, Natarajan P. Polygenic scores to assess atherosclerotic cardiovascular disease risk: clinical perspectives and basic implications. Circ Res. 2020;126(9):1159–1177. 10.1161/CIRCRESAHA.120.315928 [PubMed: 32324503]
19. Kullo IJ, Jouni H, Austin EE, et al. Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein cholesterol levels (the MI-GENES clinical trial). Circulation. 2016;133(12):1181–1188. 10.1161/CIRCULATIONAHA.115.020109 [PubMed: 26915630]
20. Brockman DG, Petronio L, Dron JS, et al. Design and user experience testing of a polygenic score report: a qualitative study of prospective users. BMC Med Genomics. 2021;14(1):238. 10.1186/s12920-021-01056-0 [PubMed: 34598685]
21. Wand H, Lambert SA, Tamburro C, et al. Improving reporting standards for polygenic scores in risk prediction studies. Nature. 2021;591(7849):211–219. 10.1038/s41586-021-03243-6 [PubMed: 33692554]

22. Lewis ACF, Green RC. Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues. Genome Med. 2021;13(1):14. 10.1186/s13073-021-00829-7 [PubMed: 33509269]
23. Polygenic risk score task force of the international common disease alliance responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. Nat Med. 2021;27(11):1876–1884. 10.1038/s41591-021-01549-6 [PubMed: 34782789]
24. Homburger JR, Neben CL, Mishne G, Zhou AY, Kathiresan S, Khera AV. Low coverage whole genome sequencing enables accurate assessment of common variants and calculation of genome-wide polygenic scores. Genome Med. 2019;11(1):1–12. 10.1186/s13073-019-0682-2 [PubMed: 30609936]
25. Neben CL, Zimmer AD, Stedden W, et al. Multigene panel testing of 23,179 individuals for hereditary cancer risk identifies pathogenic variant carriers missed by current genetic testing guidelines. J Mol Diagn. 2019;21(4):646–657. 10.1016/j.jmoldx.2019.03.001 [PubMed: 31201024]
26. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405–424. 10.1038/gim.2015.30 [PubMed: 25741868]
27. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31(3):301–306. 10.1111/j.2044-8260.1992.tb00997.x [PubMed: 1393159]
28. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. JAMA. 2018;320(19):2020–2028. 10.1001/jama.2018.14854 [PubMed: 30418471]
29. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th Edition. 2015. https://health.gov/sites/default/files/2019-09/2015-2020_Dietary_Guidelines.pdf
30. Muse ED, Chen S-F, Liu S, et al. Impact of polygenic risk communication: an observational mobile application-based coronary artery disease study. NPJ Digit Med. 2022;5(1):30. 10.1038/s41746-022-00578-w [PubMed: 35277577]
31. Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. Genet Med. 2019;21(8):1708–1718. 10.1038/s41436-018-0406-9 [PubMed: 30643217]
32. eMERGE Genomics Risk Assessment and Management Network. Genome.Gov. Accessed January 20, 2022. https://www.genome.gov/Funded-Programs-Projects/eMERGE-Genomics-Risk-Assessment-and-Management-Network
33. Our future health. Accessed January 20, 2022. https://ourfuturehealth.org.uk/
34. Marteau TM, French DP, Griffin SJ, et al. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. Cochrane Database Syst Rev. 2010;(10):CD007275. 10.1002/14651858.CD007275.pub2 [PubMed: 20927756]
35. Scheinfeldt LB, Schmidlen TJ, Gharani N, et al. Coronary artery disease genetic risk awareness motivates heart health behaviors in the Coriell Personalized Medicine Collaborative. Expert Rev Precis Med Drug Dev. 2016;1(4):407–413. 10.1080/23808993.2016.1197039
36. Weale ME, Riveros-Mckay F, Selzam S, et al. Validation of an integrated risk tool, including polygenic risk score, for atherosclerotic cardiovascular disease in multiple ethnicities and ancestries. Am J Cardiol. 2021;148:157–164. 10.1016/j.amjcard.2021.02.032 [PubMed: 33675770]
37. Aragam KG, Dobbyn A, Judy R, et al. Limitations of contemporary guidelines for managing patients at high genetic risk of coronary artery disease. J Am Coll Cardiol. 2020;75(22):2769–2780. 10.1016/j.jacc.2020.04.027 [PubMed: 32498804]

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

CAD is a leading cause of mortality, and there is an increased need for better identification of people at risk. State-of-the-art genetic risk interpretation for CAD requires assessment for both monogenic variants—such as those related to familial hypercholesterolemia—as well as the cumulative impact of many common variants, as quantified by a polygenic score. A combined monogenic and polygenic risk assessment for CAD can identify individuals at a high inherited risk for CAD, especially those harboring a familial hypercholesterolemia variant and/or with an elevated polygenic score, even before overt manifestation of traditional risk factors for CAD. Individuals who performed a combined genetic risk assessment for CAD expressed learning something valuable and developed motivation and intent to make positive lifestyle changes to reduce their risk to develop CAD. A combined monogenic and polygenic risk assessment could impact clinician decision-making on preventive interventions such as statin initiation, statin intensification, and coronary imaging to assess for existing coronary plaque and incentivize statin therapy optimization.

TRANSLATIONAL OUTLOOK:

Additional research is needed to assess the benefit and utility of integrating a combined monogenic and polygenic test into clinical risk assessment algorithms for the prevention of CAD.

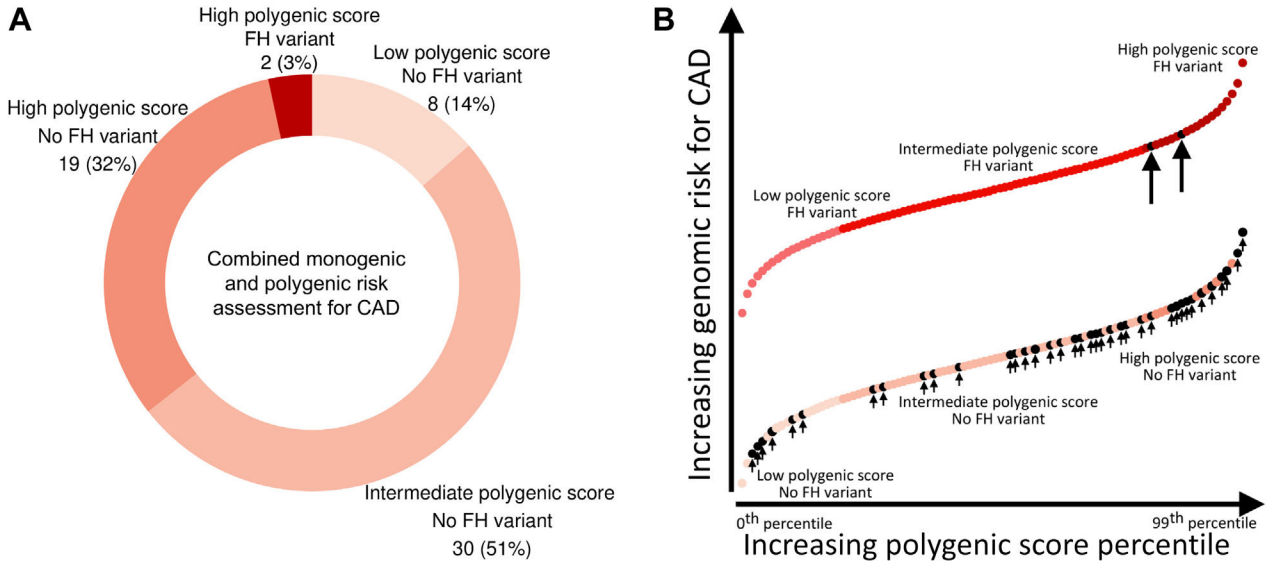


FIGURE 1. Combined Monogenic and Polygenic Risk Disclosure for Coronary Artery Disease

(A) Results of combined monogenic and polygenic risk assessment for coronary artery disease; a high polygenic score is defined as being in the 80th to 99th percentile, an intermediate polygenic score as being in the 20th to 79th percentile, and a low polygenic score as being in the 0 to 19th percentile of the population distribution of polygenic scores. **(B)** Illustration of genomic risk for coronary artery disease by polygenic score category and familial hypercholesterolemia variant carrier status. The arrows and black dots indicate the participants' genetic risk, and the larger arrows highlight the participants with both high polygenic scores and familial hypercholesterolemia variants. **B** is partially reproduced from Fahed et al.[10] CAD = coronary artery disease; FH = familial hypercholesterolemia.

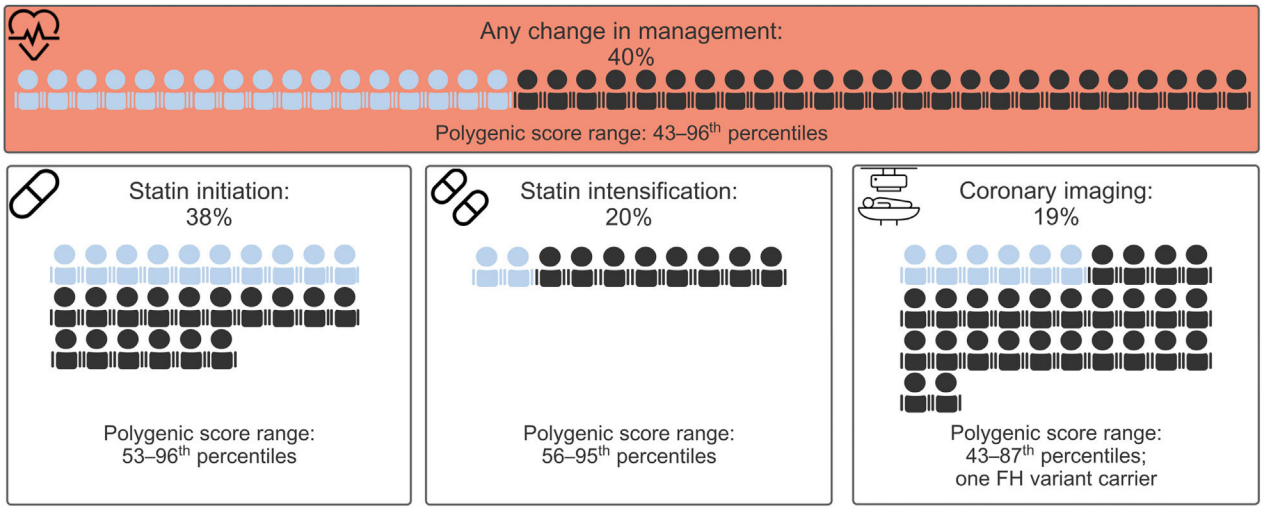
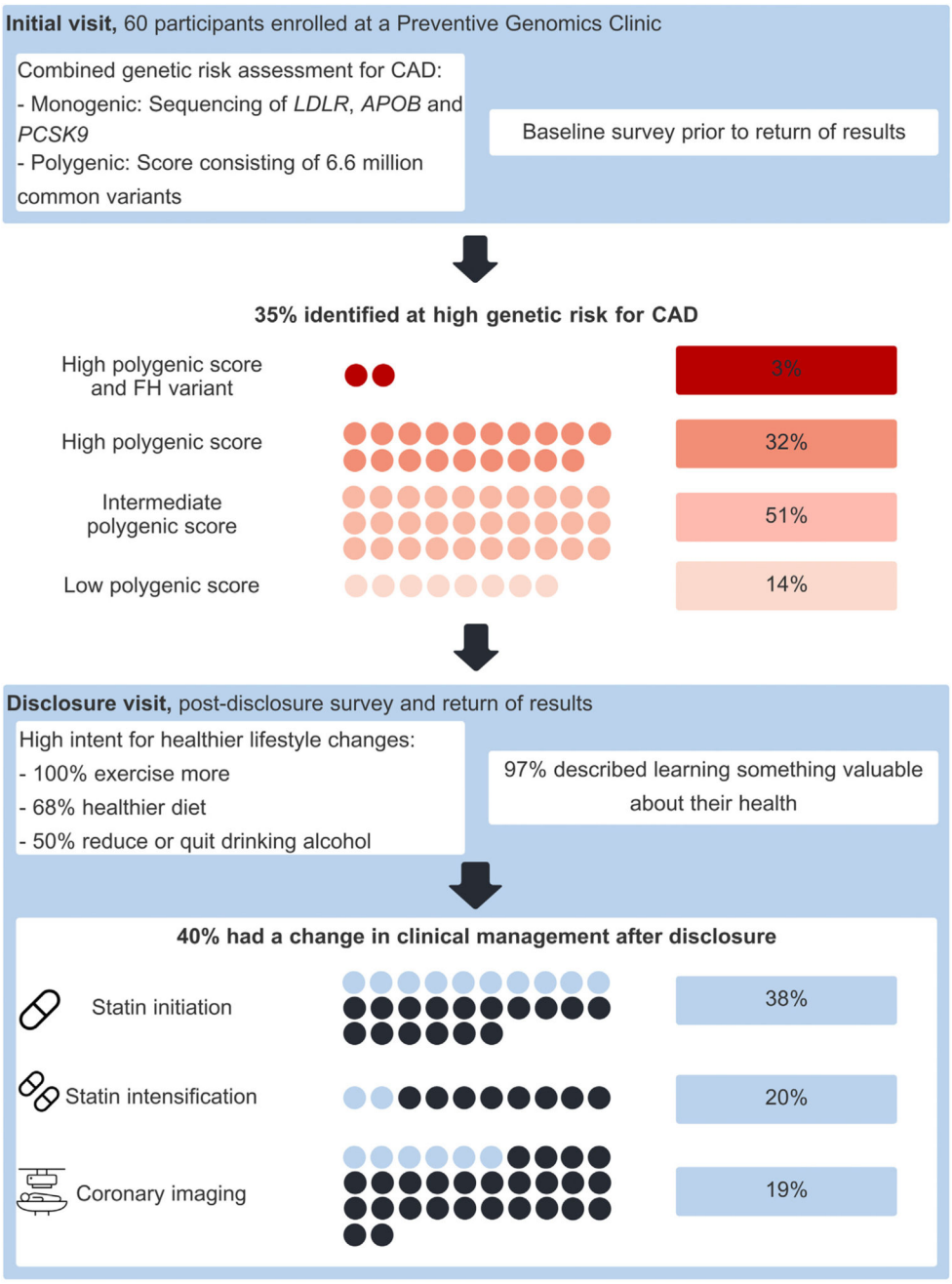


FIGURE 2. Impact of Combined Monogenic and Polygenic Risk Assessment on Clinical Management (N = 42)

Figure showing the proportion of participants without coronary artery disease who had a change in clinical management following the disclosure visit. Of the 42 participants without CAD, 17 had a change in management, including changes in pharmacotherapy and diagnostic testing. Of the 26 not on a statin at baseline, 10 (38%) were recommended to initiate statin therapy. Of the 10 on a moderate-intensity statin at baseline, 2 (20%) were recommended to increase their statin dosage. Of the 32 who did not have a coronary imaging scan in the last 5 years, 6 (19%) were recommended to undergo a coronary imaging scan. Percentages are based on the respective eligible population size. The polygenic score range shows the scores of the participants who had the respective intervention proposed. FH = familial hypercholesterolemia.



CENTRAL ILLUSTRATION. Combined Monogenic and Polygenic Risk Assessment and Disclosure Can Identify Individuals at High Inherited Risk for Coronary Artery Disease, Encourage Intent to Have a Healthier Lifestyle, and Guide Initiation of Preventive Therapy

A clinical test inclusive of both monogenic and polygenic risk for coronary artery disease was returned to participants. Three percent of participants had a monogenic variant pathogenic for familial hypercholesterolemia and 32% had a polygenic score in the top quintile of the population distribution. Participants were also asked to complete 2 surveys, 1 at baseline and 1 following disclosure of genetic test results. In the postdisclosure survey, Participants expressed intent to make positive lifestyle changes. Most participants stated

that they learned something valuable about their health. Nearly half of participants without coronary artery disease had a change in management including statin initiation, statin intensification, or coronary imaging following the Disclosure of Results. CAD = coronary artery disease.

TABLE 1

Baseline Characteristics of Study Participants

	All Participants (N = 60)	With Coronary Artery Disease (n = 17)	Without Coronary Artery Disease (n = 43)
Demographics			
Age at enrollment, y	50.83 ± 13.28	55.35 ± 13.78	49.05 ± 12.80
Female	22 (36.7)	3 (17.6)	19 (44.2)
Self-reported race and ancestry			
European	42 (70.0)	13 (76.5)	29 (67.4)
South Asian	15 (25.0)	4 (23.5)	11 (25.6)
East/Southeast Asian	2 (3.3)	0 (0.0)	2 (4.7)
Middle Eastern/North African/ West Asian	1 (1.7)	0 (0.0)	1 (2.3)
Prior genetic test done	18 (30.0)	5 (29.4)	13 (30.2)
Socioeconomic factors			
Annual household income			
<79,000, US$	2 (3.8)	0 (0.0)	2 (5.3)
80,000–139,999, US$	10 (19.2)	1 (7.1)	9 (23.7)
140,000 or more, US$	34 (65.4)	12 (85.7)	22 (57.9)
Prefer not to answer	6 (11.5)	1 (7.1)	5 (13.2)
Highest degree achieved			
Post-high school training	4 (7.7)	3 (21.4)	1 (2.6)
College degree	14 (26.9)	2 (14.3)	12 (31.6)
Graduate or professional degree	34 (65.4)	9 (64.3)	25 (65.8)
Risk factors for CAD			
Hyperlipidemia	36 (60.0)	13 (76.5)	23 (53.5)
Hypertension	11 (18.3)	5 (29.4)	6 (14.0)
Diabetes mellitus	3 (5.0)	2 (11.8)	1 (2.3)
ASCVD in a first-degree relative	40 (66.7)	13 (76.5)	27 (62.8)
10-y estimated ASCVD risk category in participants without CAD			
Low	21 (72.4)	NA	21 (72.4)
Borderline	2 (6.9)	NA	2 (6.9)
Intermediate	5 (17.2)	NA	5 (17.2)
High	1 (3.4)	NA	1 (3.4)
Lifestyle and diet			
Weekly exercise meets guidelines	44 (86.3)	14 (100.0)	30 (81.1)
Vegetable and fruit intake meets guidelines	17 (33.3)	5 (35.7)	12 (32.4)
BMI, kg/m^2	26.27 ± 5.22	25.68 ± 4.51	26.49 ± 5.50
Smoking status			
Current smoker	0 (0)	0 (0)	0 (0)
Former smoker	15 (25.0)	4 (23.5)	11 (25.6)
Never smoker	45 (75.0)	13 (76.5)	32 (74.4)
Laboratory values available at baseline	52 (86.7)	14 (82.4)	38 (88.4)

	All Participants (N = 60)	With Coronary Artery Disease (n = 17)	Without Coronary Artery Disease (n = 43)
Total cholesterol, mg/dL	177.70 ± 53.11	125.38 ± 27.72	196.08 ± 47.40
LDL-C, mg/dL	96.72 ± 43.43	57.50 ± 23.17	111.16 ± 40.18
HDL-C, mg/dL	59.86 ± 14.87	55.15 ± 18.62	61.56 ± 13.16
Triglycerides, mg/dL	104.66 ± 56.13	79.23 ± 52.13	114.38 ± 55.22
CAD and lipid-lowering therapy			
CAD at recruitment	17 (28.3)	17 (100.0)	0 (0)
Statin therapy at recruitment	33 (55.0)	16 (94.1)	17 (39.5)
Ezetimibe therapy at recruitment	1 (1.7)	1 (100.0)	0 (0.0)
PCSK9 inhibitor at recruitment	4 (6.7)	3 (17.6)	1 (2.3)

Values are mean ± SD or n (%).

ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PCE = pooled cohort equations; PCSK9= proprotein convertase subtilisin/kexin type 9.

TABLE 2

Participant Evaluation of Different Resources in Improving Their Understanding of the Genetic Test Result (N = 36)

	Not At All Helpful	Slightly Helpful	Moderately Helpful	Very Helpful	Extremely Helpful	Not Used
Discussion with clinician	0	2 (6)	2 (6)	10 (28)	22 (61)	0
Polygenic score test report	0	4 (11)	2 (6)	17 (47)	12 (33)	1 (3)
Polygenic score explainer website	0	1 (3)	5 (14)	11 (31)	12 (33)	7 (19)
Participant's independent research	0	5 (14)	13 (36)	6 (17)	7 (19)	4 (11)

Values are n (%).

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TABLE 3

Impact of Combined Monogenic and Polygenic Risk Disclosure on Intent to Pursue a Healthier Lifestyle and Diet (N = 26)

Intent	Baseline Suboptimal Lifestyle and Diet	Follow-Up Intent				
		Extremely Unlikely	Unlikely	Neutral	Likely	Extremely Likely
"Based on my genetic test results, I intend to eat a healthier diet (with more fruits and vegetables) in the next 3 mo"	Participants who did not eat vegetables and fruits as recommended by guidelines at enrollment (n = 25)	0	3 (12)	5 (20)	12 (48)	5 (20)
"Based on my genetic test results, I intend to exercise more in the next 3 mo"	Participants who exercised less than recommended at enrollment (n = 3)	0	0	0	2 (67)	1 (33)
"Based on my genetic test results, I intend to reduce/quit drinking alcohol in the next 3 mo"	Participants who drank alcohol more than recommended by guidelines at enrollment (n = 2)	0	0	1 (50)	0	1 (50)

Values are n (%).