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ORIGINAL ARTICLE

Polygenic Prediction of Nongoal Response to Statin Therapy

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BACKGROUND: Genetic differences may contribute to interindividual variability in LDL-C (low-density lipoprotein cholesterol) lowering with statin therapy. Polygenic risk scores may help identify individuals unlikely to achieve guideline-concordant LDL-C targets on statins, enabling earlier therapy intensification.

METHODS: We developed a multiancestry polygenic risk score for statin nongoal response (PRS-NGR) and evaluated its association with failure to achieve an on-statin LDL-C level of ≤70 mg/dL and with percent LDL-C reduction. This longitudinal cohort study used genotyping and electronic health record-linked data from the All of Us Research Program (2018–2025), the UK Biobank (2014–2023), and the Biobank Japan (2003–2008). Participants were statin users with at least 1 prestatin and 1 on-statin LDL-C measurement. Associations were assessed overall and by genetic ancestry, with replication in the UK Biobank and Biobank Japan.

RESULTS: The study included 46 564 participants from All of Us, 37 009 from the UK Biobank, and 3613 from Biobank Japan. In All of Us, higher PRS-NGR was associated with increased odds of nongoal response (odds ratio per SD, 1.43 [95% CI, 1.37–1.49]). Compared with the middle quintile, individuals in the top 1% had a higher risk, whereas those in the bottom 1% had a lower risk of nongoal response. Associations of PRS-NGR were consistent across African, European, and Latin American ancestry groups. Each SD increase in PRS-NGR corresponded to a 1.2-percentage-point smaller LDL-C reduction. Findings were replicated in the UK Biobank (odds ratio per SD, 2.39 [95% CI, 2.23–2.57]) and in Biobank Japan (odds ratio per SD, 1.31 [95% CI, 1.17–1.46]). Integration of PRS-NGR with guideline-based criteria identified individuals who derived a higher LDL-C% change and increased identification of statin-eligible individuals.

CONCLUSIONS: We developed and validated a multiancestry polygenic risk score that estimates the risk of nongoal LDL-C response to statin therapy. Incorporation of polygenic risk into lipid-lowering treatment paradigms may improve risk stratification and support more tailored therapy intensification strategies.

Key Words: genotype ■ humans ■ odds ratio ■ population health ■ risk assessment

Elevated LDL-C (low-density lipoprotein cholesterol) remains one of the most closely linked and modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD) worldwide.[1] Since 2013, the American College of Cardiology, American Heart Association, and the United States Preventive Services Task Force have recommended statin therapy as an effective population-level LDL-lowering strategy for ASCVD risk prevention.[2,3] The 2018 American College of Cardiology and American Heart Association guidelines on cholesterol management recommended a stepwise additive approach with alternative lipid-lowering therapies if patients are either at high ASCVD risk or on maximally tolerated statins.[4] The most updated clinical guidelines define optimal statin response through LDL-C levels, often using an LDL-C level <70 mg/dL as one of the main treatment targets.[5,6]

However, it is well documented that there is wide variation in interindividual response to statin therapy.[7]

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Nonstandard Abbreviations and Acronyms

AoU	All of Us
ASCVD	atherosclerotic cardiovascular disease
CAD	coronary artery disease
GWAS	genome-wide association study
IQR	interquartile range
LDL-C	low-density lipoprotein cholesterol
OR	odds ratio
PRS	polygenic risk score
PRS-NGR	polygenic risk score for nongoal response

While factors such as adherence, diet, and baseline LDL-C levels play a role, genetic differences have been hypothesized to contribute substantially to this variability.[8] Previous GWAS (genome-wide association studies) and candidate gene studies have sought to determine whether additional loci may influence LDL-C response to statins.[8–13] Heritability of statin response measured by LDL-C change has been previously estimated at 9% to 12%.[14,15] Polygenic risk scores (PRSs) provide a single metric for the inherited component of disease risk by integrating variants discovered from GWAS. Prior studies have investigated whether PRSs derived for coronary disease influence the clinical benefit derived from statins.[16,17] A PRS derived specifically to predict of optimal LDL-C response to statins has not been previously described. A PRS could potentially help identify lipid-lowering therapy-naive individuals who would benefit from statin initiation or, alternatively, treated individuals who are suboptimal responders and might benefit from therapy intensification or alternative therapies.

To address these needs, we developed a novel genome-wide PRS for nongoal response (PRS-NGR) that incorporates multiancestry GWAS data for LDL-C and coronary artery disease (CAD) from close to 3 million individuals. We assessed the performance of PRS-NGR in predicting goal responders in a multiancestry internal validation cohort.

METHODS

The data used in this study are not publicly available due to data access restrictions. UK Biobank data were accessed under Application Number 18177, and researchers may apply for access to UK Biobank data through the standard application process (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access). All of Us Research Program data were accessed through the Controlled Tier, which requires an approved application. Interested researchers may register and apply for access to the All of Us data through the All of Us Research Hub (https://www.researchallofus.org). We encourage researchers to apply for access to these data sets to replicate our analyses. All analytical scripts used in this study will be made publicly available on Zenodo upon publication, with a permanent DOI to ensure reproducibility. This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai. The All of Us Research Program, UK Biobank, and Biobank Japan each obtained ethics approval from their respective institutional review committees, and all participants provided written informed consent at enrollment.

Study Design and Population

PRS-NGR was constructed using the multiancestry All of Us cohort (AoU; N=414 830; data from 2018 to 2025).[18] The analytical cohort was split in half: one half for derivation and the other half for internal validation (Figure S1). The polygenic risk score was further validated in an independent UK Biobank data set (N=502 316; data from 2014 to 2023[19]) and in Biobank Japan (N=3613).[20] Descriptions of the study populations, phenotyping, and genotyping can be found in the Supplemental Methods. This research was conducted using de-identified data from the UK Biobank, the All of Us Research Program, and Biobank Japan. This study conformed to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines. This study also followed polygenic risk score reporting recommendations from Wand et al.[21]

Clinical Outcomes

In All of Us, UK Biobank, and Biobank Japan, nongoal response was defined as an on-statin LDL-C level ≥70 mg/dL.[5,6] Participants' initiation of statins was defined as the first recorded documentation of a statin, the index statin. For further details on statin and LDL-C measurement phenotype extraction, please see the Supplemental Methods.

PRS-NGR Construction

First, ancestry-stratified, trait-specific GWAS data were used to calculate multiancestry polygenic scores using PRS-csx, a Bayesian shrinkage method that adjusts SNP effect sizes while accounting for population-specific linkage disequilibrium patterns.[22] GWAS results for CAD and LDL-C were used in the final PRS-NGR construction (Figure S1; Table S1). GWAS results for on-statin LDL-C change were also considered but were not included in the final PRS-NGR construction due to nonmarginal significance across ancestries (Figure S2). There were a total of 6 scores: CAD-derived and LDL-C-derived scores for each of the 3 ancestries: African, European, and Latin American. The ancestry-specific scores were then combined into the best-performing multiancestry score using a least absolute shrinkage and selection operator regression model (R package glmnet, version 4.1.8 [R Foundation]). Further details on PRS-NGR construction are available in the Supplemental Methods.

Statistical Analysis

The associations of PRS-NGR and nongoal response status were assessed using logistic regression (where nongoal response was coded as 1 and goal response was coded as 0). PRSs were scaled to a mean of zero and 1 SD, resulting in a continuous PRS (odds ratio [OR]/SD). PRS associations were

also assessed across genetic risk percentiles (OR). Variance explained was determined using Nagelkerke R^2 (R package performance, version 0.15.1 [R Foundation]).

Logistic and linear models including polygenic scores were adjusted for age, sex, statin intensity, baseline LDL-C, and the first 16 principal components (PCs). Details of how statin intensity was defined are provided in Table S2. Model fits with polynomial terms of baseline LDL-C were assessed with log-likelihood tests and Akaike Information Criterion (Supplemental Methods and Figure S3). Follow-up time in All of Us was tabulated with the enrollment date as the entry date and February 3, 2025, as the most current follow-up date. Timing of LDL-C measurements relative to index statin exposure was summarized descriptively. In AoU, we tested the strength of PRS-NGR associations with nongoal response status and LDL-C percent change after additionally accounting for current smoking, hypertension, diabetes, prior history of CAD, and chronic kidney disease. We also removed carriers of known familial hypercholesterolemia variants as a sensitivity analysis. Carriers were defined as having at least 1 of 91 autosomal dominant familial hypercholesterolemia-causing variants previously identified in *APOB* and *LDLR* (Table S3).[23] Participants with missing covariate data were excluded from the relevant analyses.

The additional value of PRS-NGR was assessed in 2 ways: (1) whether high genetic risk categories could additionally identify weaker LDL-C percent reductions among statin-treated people and (2) whether low genetic risk categories could identify additional statin-eligible participants among statin-naive people. Individuals were categorized based on Class I statin therapy eligibility criteria from the 2019 American College of Cardiology/American Heart Association guidelines on primary prevention (Supplemental Methods).[24] Ten-year ASCVD risk predictions were calculated using PREVENT equations among participants aged 30 to 79 years without prior myocardial infarction, stroke, or heart failure.[25]

Statistical significance was defined as $P<0.05$, with 2-tailed tests, or 95% CIs that excluded the null value. Statistical analyses were performed using R, version 4.5.0 (R Foundation).

RESULTS

Population Characteristics

The study population included 46564 individuals from the AoU (median [interquartile range, IQR] age, 61 [53–68] years; 10528 female participants [45%]) and 4690 individuals from UK Biobank Primary Care linked cohort (median [IQR] age, 61 [57–65] years; 3080 female participants [66%]). Individuals were included in the study cohort if they had recorded statin use and at least 1 baseline and 1 on-statin LDL-C measurement. The total follow-up time in the study population was 47260 person-years, with a median follow-up time of 4.2 years (IQR, 2.7–5.5). The index date of statin initiation was defined as the first recorded statin use. The most common statin type used in AoU was atorvastatin (47.8%; Table S4). Of the nonstatin lipid-lowering therapies, fibrates were the most commonly used in conjunction with statins (1.3%) (Table S5). The median time from baseline LDL-C measurement to the date of index statin initiation was 62.5 days (IQR, 7.0–270.7). The median time from the date of index statin initiation to the time of the first on-statin cholesterol measurement was 207.2 days (IQR, 98.7–401.9). The median percentage of prescription completeness was 37%, which is in line with previously reported measures of statin prescription completeness in AoU.[26] Using an alternative metric, proportion of days covered, the median was 61%, which is in line with the previously reported proportion of days covered for statins.[27] Percentage of prescription completeness is lower by design because it calculates relative to the total expected number of medications. A total of 18515 (39.8%) statin users in All of Us had at least 1 statin dose change. Other statin exposure and adherence metrics can be found in the Supplemental Material (Table S6; Figure S4).

The AoU training cohort (N=19091) was composed of 20% African, 1.2% East Asian, 66% European, 12% Latino, 0.3% Middle Eastern and North African, and 0.8% South Asian individuals. The number of participants not meeting the defined goal response was 14613 (76.5%) within the training cohort, 14653 (76.7%) within the validation cohort, 2673 (94.8%) within the external UK Biobank cohort, and 3251 (89.9%) within the external Biobank Japan cohort. Within the AoU training cohort, nongoal responders on average had a higher baseline LDL-C of 130.3 mg/dL (SD=33.2) compared with goal responders at 98.1 (SD=30.6), so baseline LDL-C was adjusted for in subsequent analyses (further details are provided in the Supplemental Material). Clinical characteristics of the All of Us training cohort are outlined in Table 1. Clinical characteristics of the All of Us validation cohort, the UK Biobank external validation cohort, and the Biobank Japan external validation cohort can be found in Tables S7 through S9.

Association of PRS-NGR With Risk of Nongoal Response

Within the AoU validation cohort, PRS-NGR was associated with an OR per SD of 1.43 (95% CI, 1.37–1.49) for nongoal response and an R^2 of 0.067. Distributions of PRS-NGR are shown in Figure S5. After adjusting for hypertension, current smoking, diabetes, prior history of MI/stroke/heart failure, and chronic kidney disease, the association of PRS-NGR was largely unchanged (OR/SD, 1.42 [95% CI, 1.36–1.48]). The fully adjusted PRS-NGR had an AUC of 0.81 in the validation sample with sensitivity and specificity of 0.94 and 0.34, respectively. Those in the bottom 20% of PRS-NGR had an adjusted OR of 0.62 (95% CI, 0.54–0.71) for nongoal response compared with the remainder of the population. Those in the top 20% of PRS-NGR had an adjusted OR of 1.46 (95% CI, 1.27–1.67) for nongoal response compared with the remainder of the population. Compared with the middle quintile, the top 1% of PRS-NGR had a 2.54-fold

Table 1. Baseline Characteristics of All of Us Training Cohort

Variable	Overall, N=19 091*	Goal responder, N=4478*	Nongoal responder, N=14 613*
Age, y	59 (51–66)	63 (55–69)	58 (51–65)
Sex			
Female	9882 (52%)	1754 (39%)	8128 (56%)
Male	9209 (48%)	2724 (61%)	6485 (44%)
Ancestry			
African	3814 (20%)	824 (18%)	2990 (20%)
East Asian	238 (1.2%)	62 (1.4%)	176 (1.2%)
European	12 626 (66%)	3077 (69%)	9549 (65%)
Latino	2222 (12%)	464 (10%)	1758 (12%)
Middle Eastern	51 (0.3%)	8 (0.2%)	43 (0.3%)
South Asian	140 (0.7%)	43 (1.0%)	97 (0.7%)
Chronic kidney disease	1490 (7.8%)	590 (13%)	900 (6.2%)
Current smoker	2287 (12%)	491 (11%)	1796 (12%)
Hypertension	14 308 (75%)	3773 (84%)	10 535 (72%)
Diabetes	5682 (30%)	1848 (41%)	3834 (26%)
Prior history of MI/stroke	2239 (12%)	831 (19%)	1408 (9.6%)
Baseline LDL-C, mg/dL	123 (99–145)	99 (77–118)	130 (108–150)
On-statin LDL-C, mg/dL	90 (71–112)	58 (49–65)	99 (85–119)

LDL-C indicates low-density lipoprotein cholesterol.
*Median (Q1–Q3); n (%).

increased risk of not achieving goal response on statin therapy (OR, 2.54 [95% CI, 1.70–3.89]), and the bottom 1% of PRS-NGR had a 0.37-fold decreased risk of not achieving goal response on statins (OR, 0.37 [95% CI, 0.26–0.52]; Figure 1). We performed several sensitivity analyses to test the robustness of the overall PRS-NGR association. First, there were a total of 146 carriers of familial hypercholesterolemia autosomal dominant variants (mean baseline LDL, 158.2 mg/dL; SD, 418.2 mg/dL) within the analytic cohort, encompassing 73 of the 91 putative variants. When 77 carriers were removed from the validation cohort as a sensitivity analysis, the fully adjusted PRS-NGR was largely unchanged with an OR per SD of 1.43 (95% CI, 1.37–1.49). Second, when 1983 concomitant users of other nonstatin lipid-lowering therapies (eg, fibrates) were removed from the validation sample, the fully adjusted PRS-NGR was also largely unchanged with an OR per SD of 1.43 (95% CI, 1.37–1.49). Third, when total duration of statin treatment was included as a covariate, the fully adjusted PRS-NGR remained unchanged with an OR per SD of 1.43 (95% CI, 1.37–1.49). Fourth, when conducting a sex-stratified analysis, PRS-NGR performed similarly in men (OR/SD, 1.44 [95% CI, 1.36–1.52]) and in women (OR/SD, 1.42 [95% CI, 1.33–1.51]).

We found that the effect size in individuals with an average baseline LDL-C <100 mg/dL was an OR per SD of 1.46 (95% CI, 1.37–1.55), and the OR per SD in individuals with an average baseline LDL-C between 160 and 190 mg/dL was 1.60 (95% CI, 1.23–2.08) (Table S10 and Figure S6). In individuals who were initially prescribed a low-intensity statin, the adjusted OR per SD was 1.47 (95% CI, 1.19–1.81), and in those who were initially prescribed a high-intensity statin, the adjusted OR per SD was 1.36 (95% CI, 1.27–1.45). There was no significant difference in PRS-NGR OR per SD across baseline statin intensity categories (Table S11 and Figure S7).

Across ancestries, PRS-NGR was associated with nongoal response in African, European, and Latino subgroups (Table 2). With only 207 subjects in AoU, the PRS-NGR association in the East Asian subgroup was not statistically significant. Due to smaller subject numbers, PRS-NGR could not be computed in the Middle Eastern/North African and South Asian subgroups. The proportion of nongoal responders was 80.3% (49/61) in Middle Eastern or North African individuals and 76.4% (123/161) in South Asian individuals respectively. PRS-NGR also demonstrated the ability to risk-stratify across ancestry-based subgroups (Figure S8 and Table S12). High PRS was associated with higher risk of statin nonresponse in the Latin American subgroup (OR/SD: 2.00, 95% CI, 1.35–2.97) and in the African subgroup (OR/SD, 2.56 [95% CI, 1.88–3.52]). We formally tested for heterogeneity of the PRS effect across ancestry groups by including an interaction term between PRS-NGR and ancestry in a pooled logistic regression model. There was no evidence of heterogeneity (P=0.17), supporting consistent effects across ancestries. In clinical subgroups, PRS-NGR performance was fairly stable, with ORs per SD ranging from 1.32 to 1.50 (Figure S9). PRS-NGR was more

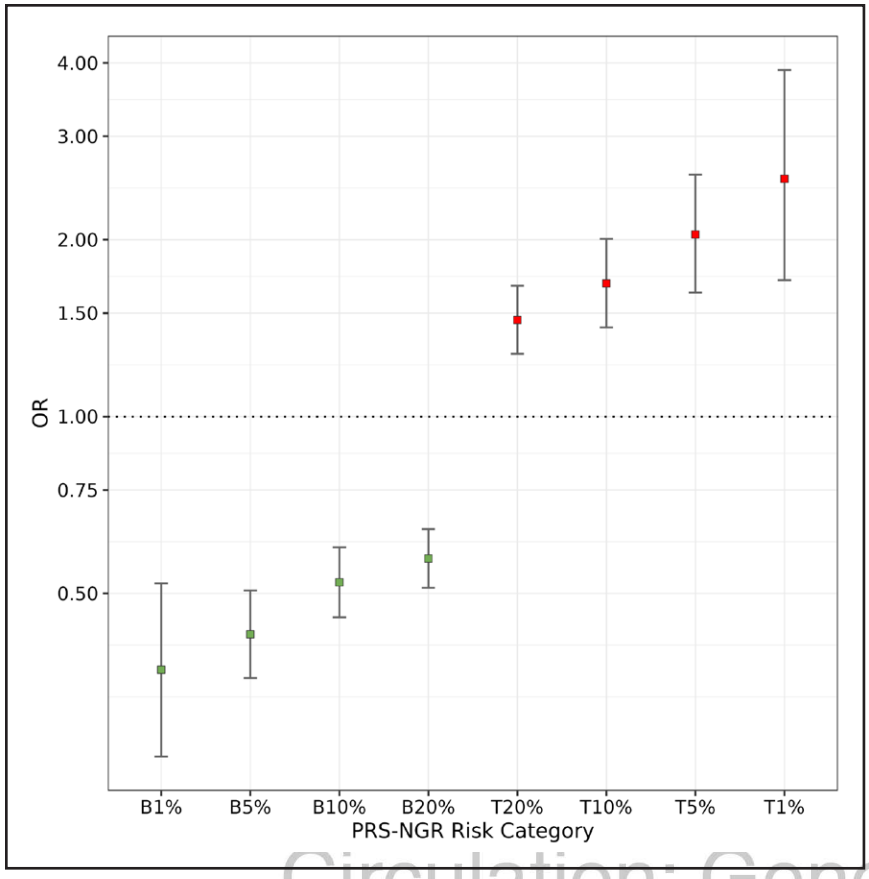

Figure 1. Polygenic prediction of nongoal response in All of Us. Estimated risk of nongoal response on statin therapy in the top (T) and bottom (B) percentiles of the polygenic risk score for nongoal response (PRS-NGR) relative to the middle quintile (40%–60%) in the All of Us validation data set. Odds ratios (ORs) were derived from logistic regression models adjusted for age, sex, statin intensity, baseline LDL-C (low-density lipoprotein cholesterol), and the first 16 principal components. Results are shown on a log axis. Error bars represent 95% CIs of the ORs. Red indicates elevated risk of being a nongoal responder. Green indicates decreased risk of being a nongoal responder.

strongly associated in patients without baseline diabetes (OR/SD, 1.50 [95% CI, 1.43–1.57]) compared with those with baseline diabetes (OR/SD, 1.32 [95% CI, 1.24–1.41]).

Association of PRS-NGR With LDL-C Percent Change

In addition to predicting binary goal responder status, we evaluated whether PRS-NGR was associated with the degree of LDL-C reduction in AoU (Figure 2). Within the AoU validation sample, every 1 SD of PRS-NGR was associated with a 1.2-percentage-point smaller reduction (−0.012 change in LDL-C% change [95% CI, −0.016 to −0.007]; $P=4.8\times10^{-7}$) from average baseline LDL-C to average on-statin LDL-C. In the lowest 10% of PRS-NGR, the median LDL-C percent reduction was 32.5% compared with the median LDL-C percent reduction of 28.6% in the highest 10% of PRS-NGR (Figure S10). The linear R^2 was 0.1%. We also considered an alternative goal-response definition based on whether patients reached a 30% LDL-C reduction threshold. Using this alternate definition, we found that PRS-NGR was still associated with an OR per SD of 1.31 (95% CI, 1.26–1.35). We also wanted to confirm that there would be a nonsignificant association of PRS-NGR with LDL-C levels in nonstatin-treated patients to show that it captures genetic liability independent of baseline LDL-C. In All of Us, PRS-NGR showed a small association with longitudinal LDL-C change (β, 0.0046 [95% CI, 0.0007–0.0084]), corresponding to a 0.46-percentage-point greater change in LDL-C per SD increase in PRS-NGR.

Table 2. Risk of Nongoal Response Associated with PRS-NGR in Ancestry Subgroups in All of Us

Ancestry	Nongoal responder, n/total N (%)	OR per SD (95% CI)	*P* value
African	3036/3899 (78)	1.50 (1.36–1.64)	<0.001
East Asian	156/207 (75)	1.29 (0.81–2.09)	0.28
European	9559/12548 (76)	1.45 (1.38–1.52)	<0.001
Latin American	1730/2212 (78)	1.23 (1.08–1.41)	<0.001

Adjusted odds ratios for nongoal response were calculated using logistic regression models adjusted for age, sex, baseline LDL-C, first 16 principal components, and statin intensity. LDL-C indicates low-density lipoprotein cholesterol; OR, odds ratio; and

PRS-NGR, polygenic risk score for nongoal response.

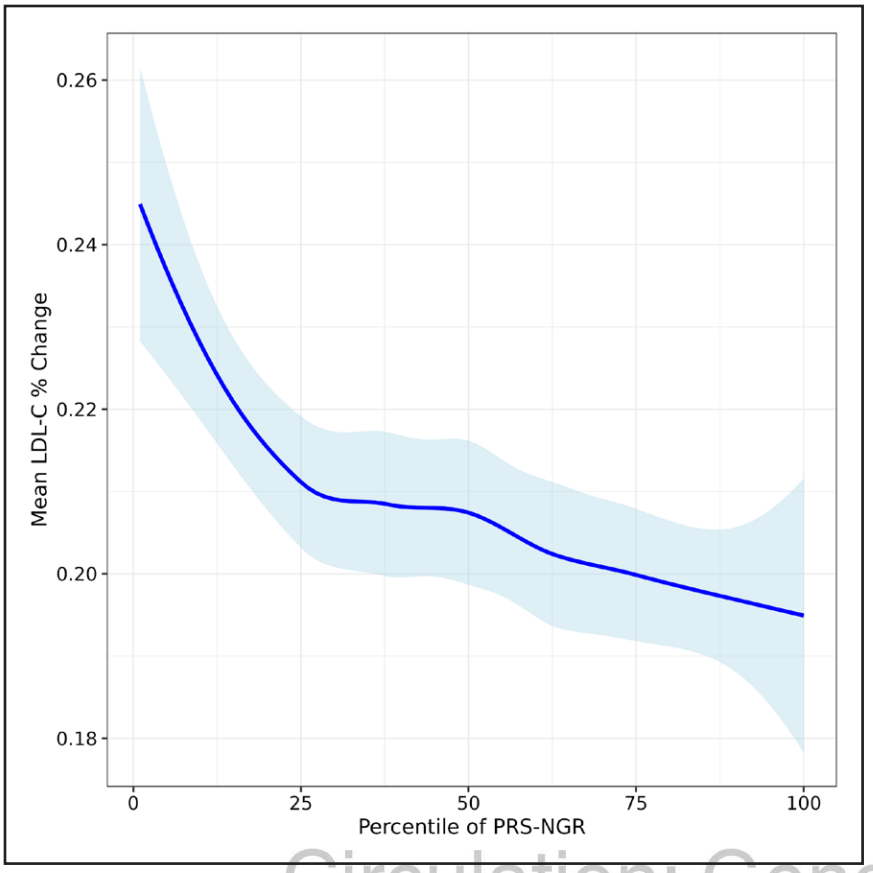

Figure 2. Polygenic risk score for nongoal response (PRS-NGR) is associated with LDL-C (low-density lipoprotein cholesterol) percent reduction.
Loess regression plot of PRS-NGR and mean LDL-C percent change in the All of Us validation data set. The shaded region represents the 95% confidence band. PRS-NGR values were residualized for age, sex, statin intensity, baseline LDL-C, and the first 16 principal components.

In UK Biobank, we observed a similarly small association (β, 0.0071 [95% CI, 0.0032–0.011]), corresponding to a 0.71-percentage-point greater change per SD increase. Although statistically significant, these effect sizes are small in magnitude.

Validation of PRS-NGR in External Cohorts

In the UK Biobank, PRS-NGR was significantly associated with increased odds of nongoal response (OR/SD, 2.39 [95% CI, 2.23–2.57]). PRS-NGR improved risk stratification in the UK Biobank when considering genetic risk categories. The highest 20% of PRS-NGR had an OR of 3.10 (95% CI, 2.80–3.44), and the middle quintile had an OR of 1.80 (95% CI, 1.67–1.94) relative to the bottom 20%. PRS-NGR was not significantly associated in the East Asian subgroup within All of Us, so it was assessed in a larger sample of East Asian ancestry individuals within the Biobank Japan cohort. Within Biobank Japan, PRS-NGR was significantly associated with a 1.31-fold (95% CI, 1.17–1.46) increased odds of nongoal response.

Integration of Polygenic Risk With Statin Initiation Guidelines

We assessed whether PRS-NGR could add incremental value to lipid-lowering therapy initiation guidelines in 2 ways.[4] We first assessed, among statin-treated people, the relationship between the addition of top PRS risk categories (higher risk of nongoal response) and LDL-C percent change (Figure 3A). We then assessed among statin-naive people, the relationship between the addition of bottom PRS risk categories (lower risk of nongoal response) and the number of eligible participants (Figure 3B). We evaluated these across 4 categories of eligibility criteria for lipid-lowering therapy initiation: those with an ASCVD risk >7.5% and baseline LDL-C between 70 and 190 mg/dL, those with a history of diabetes and baseline LDL-C between 70 and 190 mg/dL, those with baseline LDL-C >190 mg/dL, and those with a prior history of CAD. For example, statin-treated participants who had a history of diabetes had a 5.8-percentage-point smaller LDL-C percent reduction of 16.7% compared with 22.5% when integrating the top 5% of PRS-NGR. Among statin-naive participants, PREVENT-calculated ASCVD risk >7.5% eligibility criteria identified 5133 individuals who were eligible, whereas the addition of the top 10% of PRS-NGR identified an additional 586 participants, representing a 1.11-fold increase in the number of eligible people identified.

Use of Additional Lipid-Lowering Therapies

We also assessed whether PRS-NGR could identify individuals who received other lipid-lowering therapies in addition to a statin. In the entire All of Us cohort, 1113

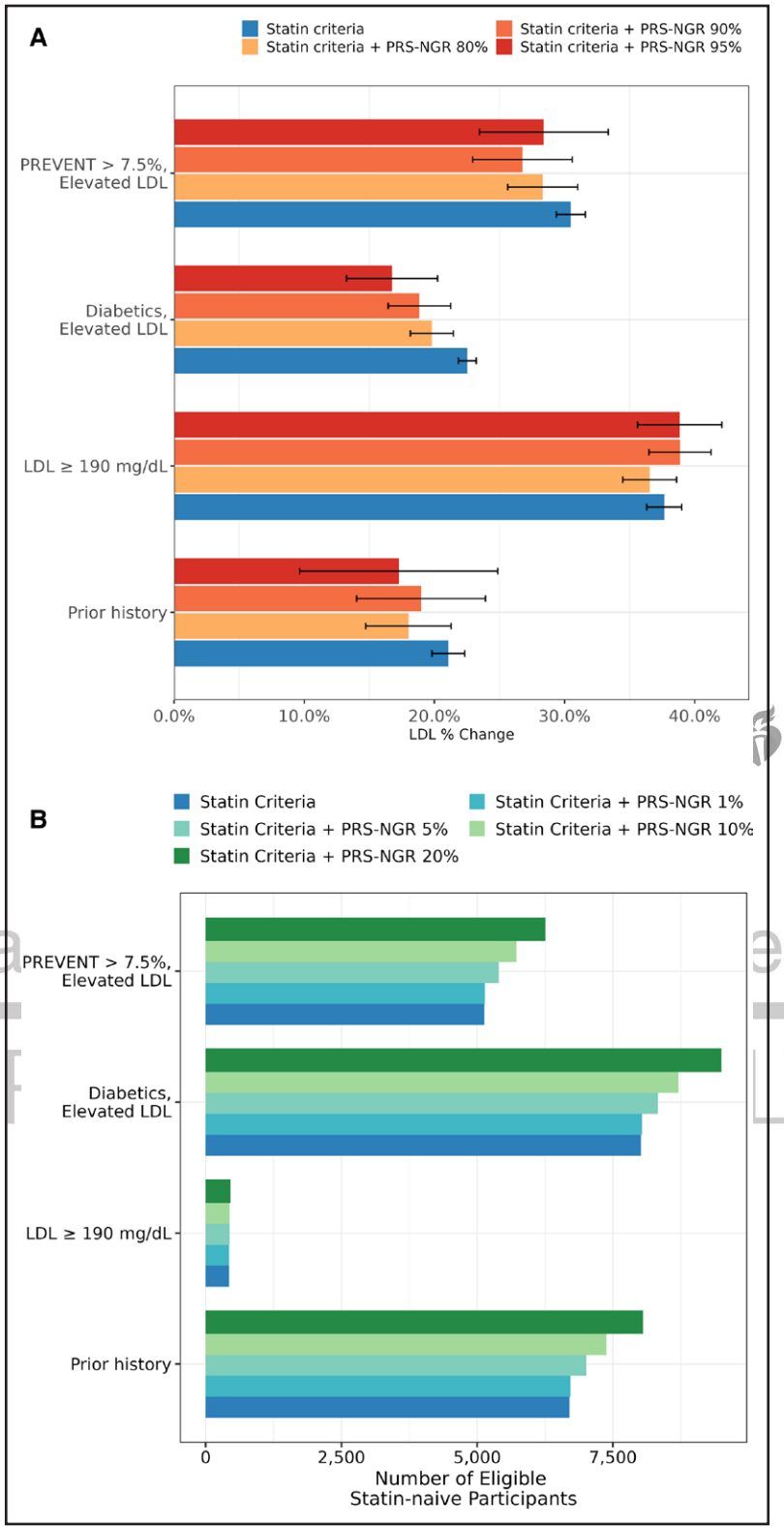

Figure 3. Polygenic risk score for nongoal response (PRS-NGR) and lipid-lowering therapy initiation criteria.
A, Mean LDL-C (low-density lipoprotein cholesterol) percent change among statin-treated individuals in All of Us, stratified by statin eligibility criteria[24] with the addition of high genetic risk categories (top 20%, top 10%, or top 5% of PRS-NGR). **B**, Number of statin-naive participants in All of Us eligible for statin therapy according to guideline-based eligibility criteria[24] with the addition of low genetic risk categories (bottom 1%, 5%, 10%, and 20% of PRS-NGR).

individuals received ezetimibe 10 mg either concomitantly with or preceding their statin (Table S5). Within the training cohort, among the top 20th percentile of PRS-NGR, 354 individuals (1.8%) received ezetimibe at any time compared with 57 individuals (0.3%) in the remainder. Within the AoU validation cohort, 423 (2.2%) individuals in the top 20th percentile received ezetimibe compared with 68 (0.36%) in the bottom 80%. A 1 SD increase in PRS-NGR was associated with 1.30-fold increased odds of ezetimibe initiation (OR, 1.31 [95% CI, 1.14–1.52]). PRS-NGR was also found to be associated with niacin initiation (OR, 1.22 [95% CI, 1.07–1.38]). PRS-NGR associations with other nonstatin lipid-lowering therapies are found in Table S13.

DISCUSSION

In this study, we developed a new polygenic score that aggregates the effects of variants in CAD and LDL-C across 3 ancestries. This novel score shows a strong association with nongoal response to statins, risk stratification, and improved transferability among non-European groups. PRS-NGR builds upon prior work investigating the genetic contribution to LDL-C response to statin therapy by incorporating multiancestry and multitrait GWAS data in score construction.[8–13] Our PRS construction method followed a framework principle of leveraging pleiotropy captured through multiple related PRSs to improve risk estimation.[28] Our PRS-NGR was able to stratify the risk of nongoal response in African and Latino individuals in AoU, and in East Asian individuals within Biobank Japan.

Lower percentiles of PRS-NGR showed the potential of augmenting identification of statin-naive individuals who are genetically predicted to be optimal responders, which is not captured by current American College of Cardiology/American Heart Association statin eligibility criteria. Currently, guidelines outline 4 eligible groups for initiation of statins: prior myocardial infarction or stroke, LDL cholesterol levels ≥190 mg/dL, diabetes among adults aged 40 to 75 years with LDL cholesterol levels between 70 and 189 mg/dL, or predicted ASCVD risk ≥7.5% among adults aged 40 to 75 years with LDL cholesterol levels between 70 and 189 mg/dL.[24] When incorporated with eligibility criteria, the addition of low polygenic risk of nonoptimal response identified 586 additional eligible individuals when considering the bottom 10% and 1120 additional eligible individuals when considering the bottom 20% within All of Us. Targeted PRS testing could identify more individuals who are optimal responders and facilitate earlier initiation of statin therapy. Recent data suggest that statins remain broadly underprescribed within the US population,[29,30] but simultaneously increasing within the Medicare population.[31] Prior work has investigated how changes to risk stratification would affect the number of statin-eligible individuals.[32] While expanding indications for statins may improve population-wide lipid control, contributing to decreased ASCVD burden, overtreatment in low-risk populations may result in adverse effects, such as increased diabetes risk.[33]

On the other hand, the higher percentiles of PRS-NGR demonstrated the potential to identify individuals who will not respond optimally to statins. In our analysis of individuals at high genetic risk, PRS-NGR was associated with a higher likelihood of not meeting target LDL thresholds as well as a smaller on-statin LDL reduction. Furthermore, among individuals who had higher percentiles of PRS-NGR, there was a higher rate of ezetimibe use. Addition of ezetimibe to statins as an approach to reduce residual cardiovascular risk, intensify lipid-lowering therapy in high-risk individuals, or provide an alternative therapy to individuals affected by statin-related adverse effects or intolerance has been shown to effectively lower LDL-C and the risk of cardiovascular events.[34,35]

Based on our results, PRS-NGR testing would seem to show promise as a clinical screening tool to identify individuals who are at high genetic risk for being poor responders to statin therapy. Conceivably, these predicted poor responders could be candidates to receive additional (nonstatin) lipid-lowering therapy at the outset of therapy initiation, such as ezetimibe or even a PCSK9 inhibitor. Previous work using trial data has shown that genetic risk scores are able to identify subgroups who derive greater benefit from lipid-lowering therapies ranging from statins[17] to evolocumab.[36] Future research at the population biobank scale should continue to address the prospective effect of polygenic scores on LDL-C lowering and cardiovascular events to examine whether those at high genetic risk for nonresponse can derive a greater clinical benefit from alternative therapies such as PCSK9 inhibitors[37] or PCSK9 inhibitor monoclonal antibodies.[38,39]

Regarding next steps toward clinical implementation, several key milestones must be addressed. First, prospective validation of PRS-NGR in clinical trial settings is needed to establish whether genetically predicted poor responders derive greater benefit from upfront initiation of more aggressive LDL-lowering therapy (eg, high-dose statin plus ezetimibe, PCSK9 inhibitor) compared with conventional stepwise intensification. Second, integration of PRS-NGR into clinical decision support tools within electronic health record systems would facilitate real-time, point-of-care risk stratification at the time of statin prescribing. Third, health economic analyses comparing PRS-guided therapy selection against standard of care are warranted to evaluate cost-effectiveness before broad adoption. Finally, equitable implementation will require ensuring adequate PRS performance across diverse ancestral populations, which our multiancestry framework begins to address but must be further validated in underrepresented groups.

Limitations

Our study has several limitations. First, a key limitation is that our definition of statin nonresponse, based on failure to achieve an LDL-C threshold, is inherently dependent on baseline LDL-C levels. Individuals with higher baseline LDL-C are less likely to reach a fixed treatment target, even if they experience clinically meaningful reductions in LDL-C. In our cohort, baseline LDL-C differed between responders and nonresponders, which may contribute to the observed associations. To mitigate this, we performed complementary analyses using continuous measures of LDL-C reduction and stratified analyses by baseline LDL-C, which yielded consistent results; however, residual dependence on baseline LDL-C cannot be fully excluded. Second, although we systematically defined statin utilization and baseline and on-statin cholesterol measurements, statin utilization patterns are imperfectly captured in electronic health records, and time-varying changes were not fully modeled. In addition, appropriately measuring adherence in observational data can be difficult, and warrants further research into benchmarking adherence phenotyping algorithms.[40] Third, although we used a large multiancestry biobank, All of Us, the discovery GWAS data were largely Eurocentric. This study was also restricted to single-ancestry individuals and had limited cases from East Asian, South Asian, and Middle Eastern and North African groups. Fourth, given that statin use has been found to be associated with increased incident ASCVD risk in observational studies likely reflecting confounding by nonrandom allocation, future studies should repeat the PRS analysis in trial data. Fifth, hard 10-year cardiovascular outcomes were unavailable for statin-naive patients, so the clinical utility of identifying concordance between genetically predicted optimal responders and observed response could not be assessed.

Conclusions

This population biobank cohort study showed that a novel polygenic risk score stratified the risk of nongoal response to statin therapy across multiple ancestries. PRS-NGR also identified additional individuals as genetically predicted optimal responders when added to statin initiation eligibility criteria. These results lay the groundwork for leveraging polygenic scores to optimize cardiovascular pharmacotherapies.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

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