Validating Orchid's Rheumatoid Arthritis Genetic Risk Score

ORCHID

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation of the joints, driven by an immune response to the body's own proteins. It commonly causes joint pain, swelling, stiffness, and progressive joint damage. It can lead to irreversible disability and complications affecting the lungs, heart, and blood vessels if inadequately treated. Women are more likely to develop RA than men, and exposure to smoking can increase risk.[1]

RA affects approximately 2.65% of adults in the US.[2] Treatment of rheumatoid arthritis focuses on starting effective therapy early and adjusting it over time to reduce inflammation, prevent joint damage, and maintain physical function. Current strategies aim for remission or, if that is not achievable, low disease activity through regular monitoring and timely changes in treatment. Although RA cannot yet be cured, modern treatment approaches have substantially improved symptoms, long-term outcomes, and quality of life for most patients.[1]

Genetic Risk Score

RA is shaped by both environmental and genetic factors. Monogenic testing is not available because no single gene causes the condition. Genetic risk scores (GRS), which combine the small effects of many variants into a single score, are currently the only way to estimate genetic risk. Although not diagnostic, a GRS can indicate how likely an individual is to develop the disease.

Orchid's RA GRS was trained following current industry standards.[3,4] The GRS was constructed using the SBayesRC algorithm trained on publicly available FinnGen and Million Veterans Program summary statistics.[5,6] The summary statistics include 30,321 cases and 925,695 controls.[7] The resulting GRS contains over a million variants.

Risk predictions are adjusted to each individual's ancestry, with predictive power decaying as genetic distance from the predominately European training data increases.[8] Orchid considers a GRS meaningfully predictive if individuals at roughly the 97.7th percentile have an odds ratio (OR) of at least 2. The RA GRS meets this criterion for all common ancestry groups.

Evaluation on UK Biobank Data

We evaluated the predictive accuracy of Orchid's RA GRS using the UK Biobank (UKB), a research database of roughly 500,000 genotyped individuals from the United Kingdom.[9]

We restricted the analysis to participants of British ancestry and defined RA using the M05.x ICD-10 code, yielding 1,015 cases and 407,505 controls (0.2% prevalence). We then grouped individuals by GRS percentile and compared the observed disease prevalence within each group to our model's predictions (Figure 1). For additional technical details, see the Supplementary Information.

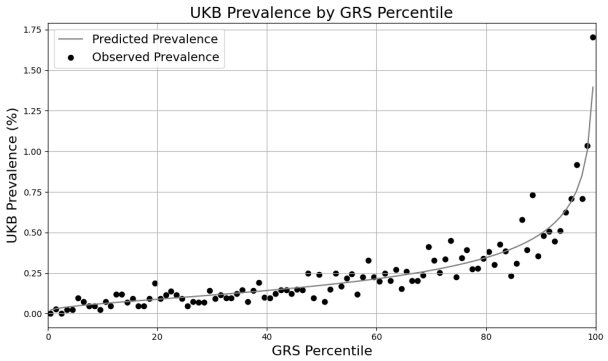

Figure 1. Risk Stratification. Predicted and observed prevalence in the UKB for individuals grouped by GRS percentile.

Table 1 shows the RA observed prevalence for individuals in the UKB grouped by GRS percentile range (top 10%, 5%, and 1%), as well as how their risk compares to the baseline risk at the 50th GRS percentile. Those with higher GRS relative to the population baseline also had substantially higher observed prevalence of RA, supporting the predictive accuracy of the GRS to identify individuals with elevated risk.

GRS Group	Observed UKB Prevalence	Odds Ratio
Baseline (50th percentile)	0.16%	1.00
Top 10%	0.80%	5.10
Top 5%	1.05%	6.70
Top 1%	1.71%	10.92

Table 1. Observed prevalence of RA in the UKB by GRS percentile range. Those with higher GRS relative to the population baseline also had substantially higher observed prevalence of RA.

Estimating Lifetime Risk

The average observed prevalence of RA in the UKB was 0.2%. This is considerably lower than the lifetime prevalence in the US general population, which has been estimated to be approximately 2.65%.[2] This is likely due in part to

the fact that UKB participants tend to be healthier than the general population, which leads to lower observed disease prevalence.[10] Additionally, the observed prevalence in the UKB includes people still living who could develop the disease when they are older, and so does not capture the full lifetime risk of the disease.

Orchid's clinical reports include predicted lifetime disease risk, which we calculate by first estimating how disease risk varies across GRS in the UKB and then rescaling that pattern so the average matches the known lifetime population risk (Figure 2).[11] People at the high end of the GRS distribution are predicted to have an elevated lifetime risk of the disease relative to the population (Table 2).

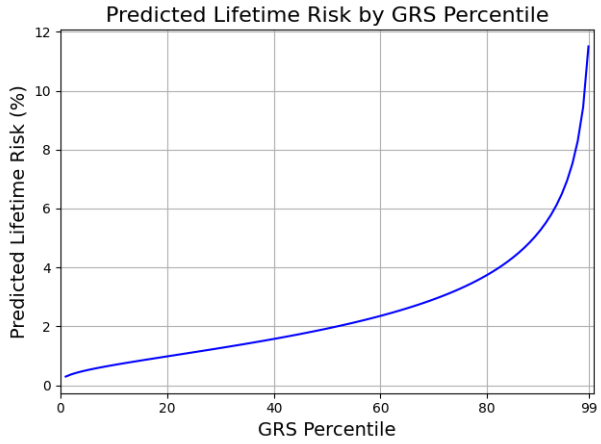

Figure 2. Adjusted Risk Stratification. Predicted risk estimates adjusted so that overall prevalence matches the 2.65% estimate.[2]

GRS Percentile	Predicted Lifetime Risk	Relative Risk
50th (baseline)	1.96%	1.00x
95th	7.08%	3.61x
97th	8.45%	4.30x
99th	11.71%	5.96x

Table 2. Predicted lifetime prevalence of RA at different GRS percentiles. Individuals with the highest GRS percentiles are predicted to have an increased risk of RA relative to those at the 50th percentile.

Conclusion

In this study, we evaluated our RA GRS on data from the UKB. We found that it performed well, particularly for identifying individuals with elevated risk of the disease relative to the population. In our embryo and couple reports, we adjust the model to predict lifetime risk, which is generally higher than observed prevalence in the UKB. The RA GRS model is available to individuals of all ancestry groups.

Acknowledgments

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References

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Supplementary Information

Baseline Risk	OR per SD	OR per 2 SD
1.96%	2.25	5.08

Table 3. OR per SD. The baseline risk for an individual with a median GRS, and the predicted OR at one and two SDs, respectively. A GRS must have a predicted OR >2 at 2 SD to be included in Orchid's clinical reports.

UKB Prevalence	Population Prevalence	Liability R^2
0.2%	2.65%	13.21%

Table 4. Liability R^2. The estimated liability R^2 using a population prevalence of 2.65%.

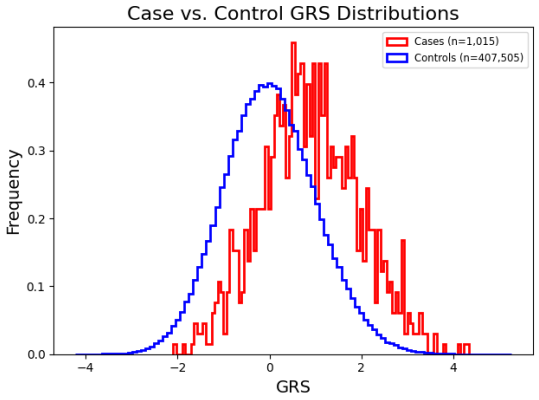

Figure 3. GRS histograms. GRS distributions for cases and controls. Both are approximately normal, with the case distribution shifted noticeably higher compared to the controls.

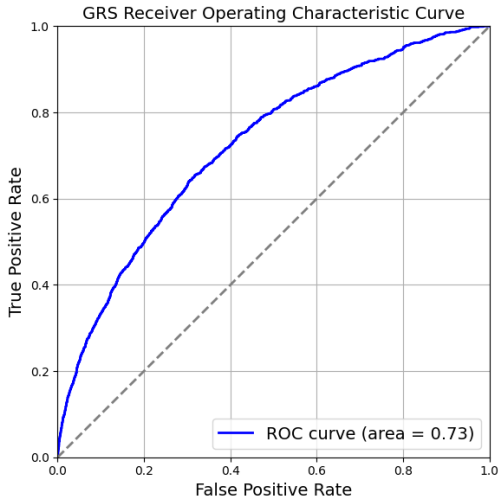

Figure 4. The receiver operating characteristic (ROC) used to compute the ROC area under the curve (AUC). The ROC curve is a graphical representation of a binary classifier's performance, plotting the True Positive Rate (TPR) against the False Positive Rate (FPR) across different decision thresholds. A curve closer to the top-left indicates a better model, while a diagonal line (AUC = 0.5) represents random guessing.

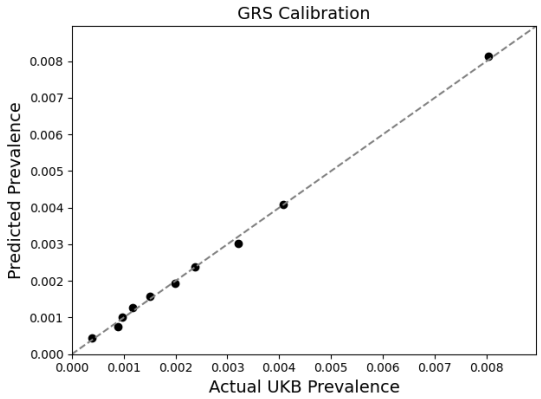

Figure 5. Calibration Curve. Calibration plot showing observed disease prevalence versus predicted risk across GRS deciles.