Validating Orchid's Psoriasis Genetic Risk Score

ORCHID

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Introduction

Psoriasis is an inflammatory disease that primarily affects the skin. The most common subtype, plaque psoriasis, accounts for up to 90% of cases and presents as red, scaly skin lesions with silvery scale. Other forms include guttate, pustular, and erythrodermic psoriasis. Up to 30% of individuals with psoriasis also develop psoriatic arthritis, and psoriasis is associated with an increased risk of cardiovascular disease, metabolic syndrome, and psychiatric conditions, though the underlying connections are not fully understood. Viral infections are a common trigger for psoriasis flares.[1]

Psoriasis affects approximately 3% of U.S. adults.[2] Treatment focuses on reducing inflammation, controlling symptoms, and preventing flares, with options ranging from topical treatments for mild disease to light-based therapies and systemic treatments for more severe cases. Lifestyle measures and trigger management are also important, and treatment is usually tailored to disease severity and impact on quality of life.[1]

Genetic Risk Score

Psoriasis is shaped by both environmental and genetic factors. Some rare variants in genes such as IL36RN are strongly associated with certain subtypes of psoriasis,[1] but most cases arise from the combined effects of many genetic variants and environmental exposures. 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 psoriasis 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 32,555 cases and 1,085,410 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 psoriasis GRS meets this criterion for all common ancestry groups.

Evaluation on UK Biobank Data

We evaluated the predictive accuracy of Orchid's psoriasis 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 psoriasis using the L40.x ICD-10 code, yielding 4,286 cases and 404,234 controls (1.0% 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.

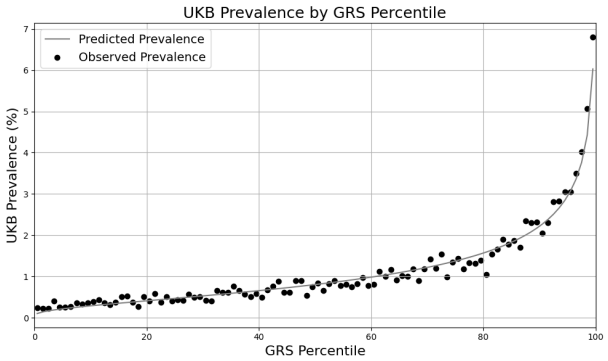

Figure 1. Risk Stratification. Predicted and observed prevalence in the UKB for individuals grouped by GRS percentile.

Table 1 shows the psoriasis 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 psoriasis, supporting the predictive accuracy of the GRS to identify individuals with elevated risk.

GRS Group	Observed UKB Prevalence	Odds Ratio
Baseline (50th percentile)	0.80%	1.00
Top 10%	3.46%	4.47
Top 5%	4.41%	5.75
Top 1%	6.81%	9.11

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

Estimating Lifetime Risk

The average observed prevalence of psoriasis in the UKB was 1%. This is somewhat lower than the lifetime prevalence

in the US general population, which has been estimated to be approximately 3%.[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).

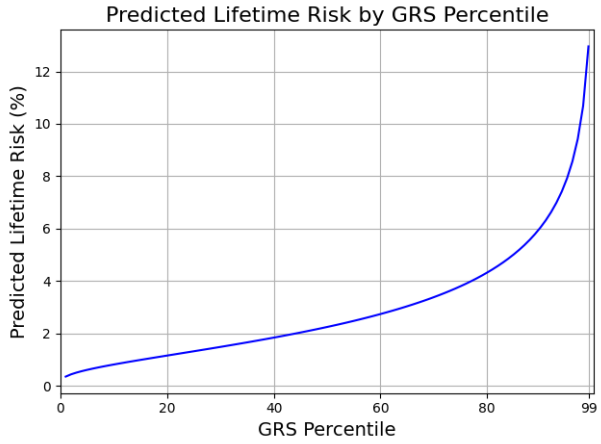

Figure 2. Adjusted Risk Stratification. Predicted risk estimates adjusted so that overall prevalence matches the 3% estimate.[2]

GRS Percentile	Predicted Lifetime Risk	Relative Risk
50th (baseline)	2.25%	1.00x
95th	7.93%	3.53x
97th	9.43%	4.20x
99th	12.96%	5.77x

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

Conclusion

In this study, we evaluated our psoriasis 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 psoriasis 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
2.25%	2.23	4.98

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
1.0%	3.0%	10.50%

Table 4. Liability R^2. The estimated liability R^2 using a population prevalence of 3%.

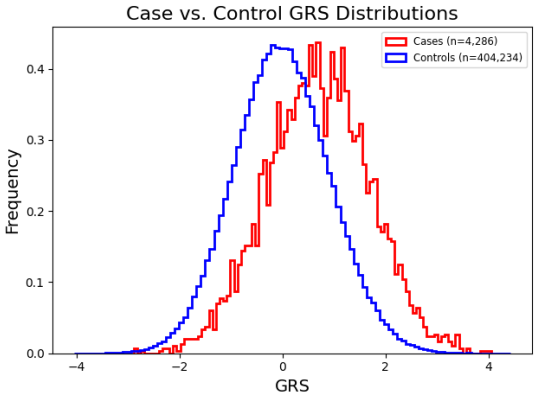

Figure 3. GRS histograms. GRS distributions for cases and controls. Both are approximately normal, with the case distribution shifted noticeably higher compared to the controls.

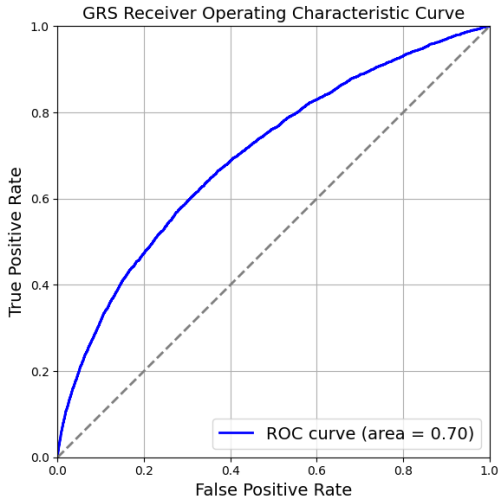

Figure 4. The receiver operating characteristic (ROC) used to compute the ROC area under the curve (AUC). The ROC curve is a graphical representation of a binary classifier's performance, plotting the True Positive Rate (TPR) against the False Positive Rate (FPR) across different decision thresholds.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

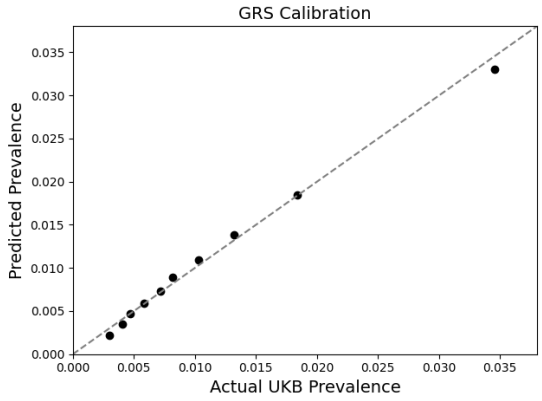

Figure 5. Calibration Curve. Calibration plot showing observed disease prevalence versus predicted risk across GRS deciles.