

Validating Orchid's Testicular Cancer Genetic Risk Score

ORCHID

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Introduction

Testicular cancer is a disease in which cancer cells form in the tissues of one or both testicles. It is the most common cancer in men between the ages of 20 and 34.¹ According to the National Cancer Institute, approximately 0.4% of men will be diagnosed with testicular cancer during their lifetime.²

Some treatments for testicular cancer can cause permanent infertility, and patients who may wish to have children are often advised to consider sperm banking before treatment.³ The five-year relative survival rate for testicular cancer is 94.6%.²

Genetic Risk Score

Testicular cancer is thought to be shaped by both environmental and genetic factors. No single high-penetrance gene is known to account for most inherited cases, and studies suggest that much of its inherited risk is polygenic.⁴ Genetic risk scores (GRS), which combine the small effects of many variants into a single score, can be used to estimate genetic susceptibility. Although not diagnostic, a GRS can indicate how likely an individual is to develop the disease.

The testicular cancer GRS included in Orchid's reports was sourced from the PGS Catalog, an open database of published GRS models (PGS000796, Kachuri et al.), and contains 52 variants.^{5,6}

Risk predictions are adjusted to each individual's ancestry, with predictive power decaying as genetic distance from the predominantly European training data increases.⁷ Orchid considers a GRS meaningfully predictive if individuals at approximately the 97.7th percentile have an odds ratio (OR) of at least 2. The testicular cancer GRS meets this criterion for all common ancestry groups.

Evaluation on UK Biobank Data

We evaluated the predictive accuracy of Orchid's testicular cancer GRS using the UK Biobank (UKB), a research database of roughly 500,000 genotyped individuals from the United Kingdom.⁸ We restricted the analysis to males of British ancestry and defined testicular cancer using the C62 ICD-10 code in the UKB's linked cancer registry data or a self-report of testicular cancer, yielding 812 cases and 186,853 controls (0.43% 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.

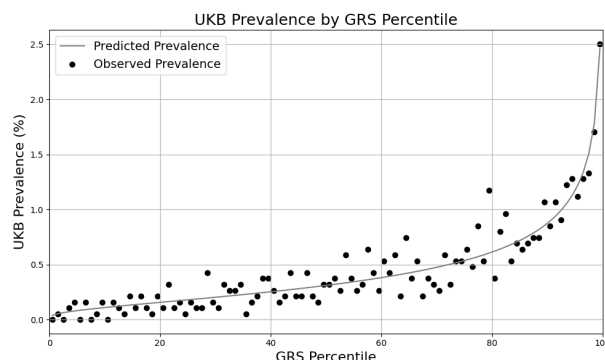


Figure 1. Risk Stratification. Predicted and observed prevalence in the UKB for individuals grouped by GRS percentile.

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

GRS Group	Observed UKB Prevalence	Odds Ratio
Baseline (50th percentile)	0.32%	1.00
Top 10%	1.33%	4.19
Top 5%	1.59%	5.03
Top 1%	2.50%	8.01

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

Estimating Lifetime Risk

According to the National Cancer Institute, approximately 0.4% of men will be diagnosed with testicular cancer during their lifetime,² similar to the observed prevalence of 0.43% in the UKB. In order to be consistent with our GRS analysis pipeline, we adjust our model so that its average prevalence exactly aligns with the National Cancer Institute estimate

(Figure 2).⁹ People at the high end of the GRS distribution are predicted to have an elevated risk of testicular cancer relative to the population (Table 2).

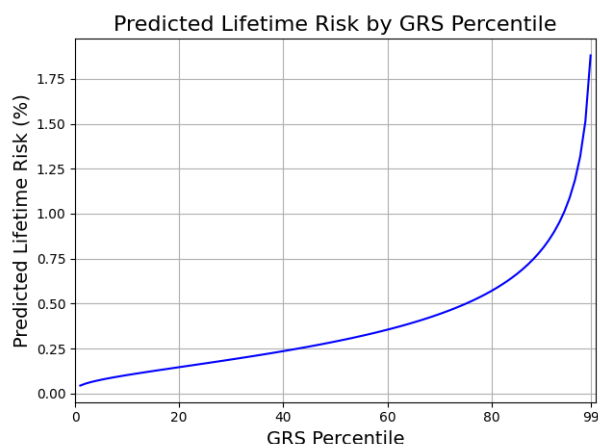


Figure 2. Adjusted Risk Stratification. Predicted risk estimates adjusted so that overall prevalence matches the 0.4% estimate from the National Cancer Institute.²

GRS Percentile	Predicted Lifetime Risk	Relative Risk
50th (baseline)	0.29%	1.00x
95th	1.09%	3.77x
97th	1.32%	4.56x
99th	1.88%	6.50x

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

Conclusion

In this study, we evaluated our testicular cancer GRS on data from the UKB. We found that it performed well, particularly for identifying individuals with elevated risk of testicular cancer relative to the population. In our embryo and couple reports, we adjust the model to predict risk consistent with the prevalence estimated by the National Cancer Institute.² The testicular cancer 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
0.29%	2.25	5.07

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
0.43%	0.4%	7.10%

Table 4. Liability R^2 . The estimated liability R^2 using a population prevalence of 0.4%.

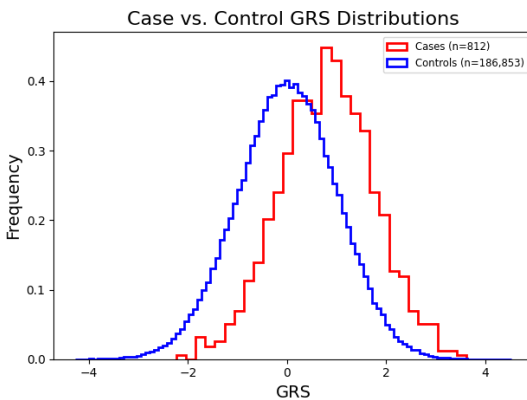


Figure 3. GRS histograms. GRS distributions for cases and controls. Both are approximately normal, with the case distribution shifted noticeably higher compared to the controls.

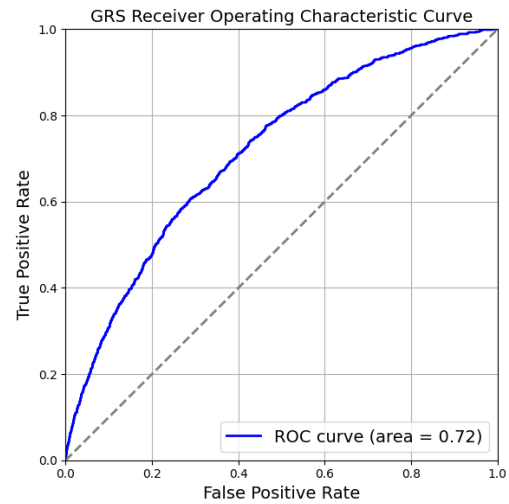


Figure 4. The receiver operating characteristic (ROC) used to compute the ROC area under the curve (AUC). The ROC curve is a graphical representation of a binary classifier's performance, plotting the True Positive Rate (TPR) against the False Positive Rate (FPR) across different decision thresholds.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

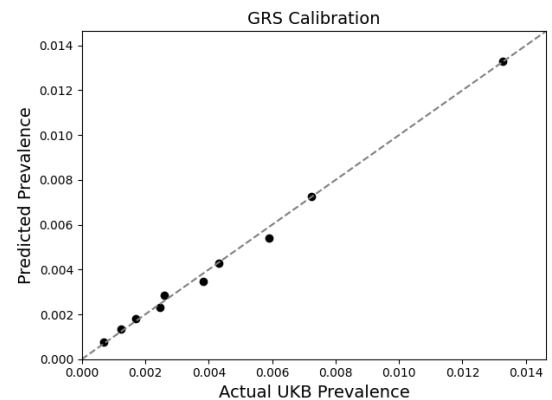


Figure 5. Calibration Curve. Calibration plot showing observed testicular cancer prevalence versus predicted risk across GRS deciles.