# Genetics vs clinical risk scores for melanoma prediction

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## Abstract

**Background**: Cutaneous melanoma is a common cancer, for which risk stratification has been proposed to aid early detection.

**Objectives**: To assess the performance of a polygenic risk score (PRS) in predicting risk for invasive cutaneous melanoma, alone and combined with clinical risk factors.

**Methods**: The PRS was derived from the most recent genome-wide association study (GWAS) meta-analysis of cutaneous melanoma, which included 28,849 melanoma cases and 78,922 controls from 20 studies from United Kingdom, United States, Australia, and Europe. Then it was tuned in the Canadian Longitudinal Studying on Aging (CLSA) cohort, which included 528 melanoma cases and 17,787 controls. The PRS was then tested independently against 14 self-reported clinical factors in the QSkin prospective cohort, which included 16,282 participants with genetic data aged 40-69 years at baseline, among whom 359 participants were identified with new invasive melanomas during 10 years of follow up.

**Results**: The PRS outperformed any other single clinical risk factor in QSkin (c-index 0.643). The baseline risk model (age, sex, first 10 principal components) had a c-index of 0.603; adding PRS to the baseline model increased the c-index to 0.670 (likelihood ratio test (LRT) $p=1.68 \times 10^{-21}$). Adding PRS to a clinical prediction model (the MP16 model) significantly enhanced discrimination (MP16 c-index: 0.713, PRS + MP16 c-index: 0.729 (median LRT $p = 5.56\times10^{-11}$)), and predicted more true cases (111 for PRS + MP16 vs 104 for PRS in the 1st decile), which is corresponding to a net reclassification improvement of 0.02.

**Conclusions**: Incorporating genetic risk information into existing clinical risk tools significantly improves prediction performance for melanoma.