

A Polygenic Risk Model for Hereditary Cancer Syndromes

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ABSTRACT

Polygenic background modifies penetrance in hereditary cancer. We built a polygenic risk model in 18,000 carriers of high-penetrance variants across five syndromes. Polygenic score shifted lifetime risk by up to 31 percentage points within the same monogenic genotype, with the largest effect in Lynch syndrome. Incorporating polygenic background materially changes surveillance recommendations.

KEYWORDS

polygenic risk score, hereditary cancer, Lynch syndrome, penetrance

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