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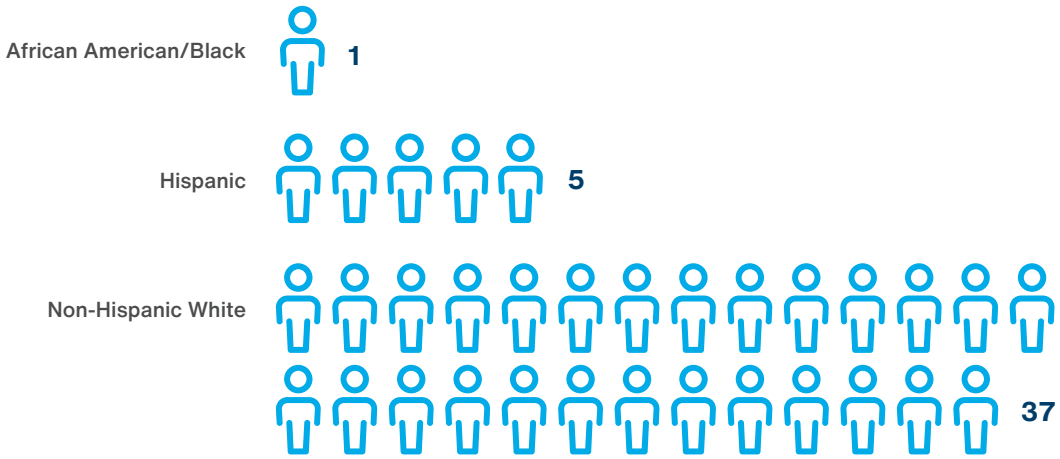
Research For Your Practice

How Race, Ethnicity, and Ancestry Can Influence Clinical Presentation and Variant Interpretation: Lessons from *CDKN2A*

INTRODUCTION

Historically, hereditary cancer syndrome characterization has relied heavily on data derived from non-Hispanic White (NHW) cohorts. However, performing variant interpretation across diverse populations using cancer penetrance estimates derived from homogenous datasets can introduce significant bias and limit clinical validity. For example, population-based data in the U.S. reveal significant variation in melanoma risk based on race and ethnicity. The annual incidence among non-Hispanic White (NHW) individuals is roughly 37 to 40 per 100,000, compared to 4.5 to 4.9 per 100,000 among Hispanic individuals and 1.0 per 100,000 among Black individuals[1] (Figure 1). However, data on how these differences in baseline risk translate to inherited predisposition are limited. To address this gap, a study published in *Genetics in Medicine* by researchers at Ambry Genetics explored the impact race, ethnicity, and ancestry (REA) has on phenotype among individuals with *CDKN2A* variants[2]. Their findings reveal important differences in how cancer risks manifest across REA groups, influencing how evidence for variant interpretation should be weighted.

Figure 1. Annual Incidence of Melanoma by Ethnicity



LEVERAGING A DIVERSE COHORT

The study consisted of nearly 200,000 consecutive individuals who underwent multigene panel testing at a single laboratory between 2015-2020. While the majority of existing *CDKN2A* data is derived from European cohorts, this dataset serves as a valuable supplement to the literature by including a significant proportion of individuals from underrepresented ancestries. A total of 519^ individuals with *CDKN2A* pathogenic or likely pathogenic variants (PVs) were identified and compared to 785 wildtype (WT) controls. One variant in particular, p.I49T, was enriched in underrepresented* (UR) REA groups and appeared to to be associated with lower risks of melanoma compared to NHW (Figure 2).

Figure 2. *CDKN2A* Genotypes Included in Study

	Typical PVs	p.I49T	Wildtype (WT)
non-Hispanic White (NHW)	287 (85.9%)	18 (9.7%)	474 (60.4%)
Underrepresented* (UR)	47 (14.1%)	167 (90.3%)	311 (39.6%
Total	334	185	785

^ Published manuscript includes one additional atypical PV, p.E69G (n=21)
* Includes African American/Black, Ashkenazi Jewish, Asian, Hispanic, Middle Eastern, and Multiple REA

HOW REA IMPACTS CLINICAL PRESENTATION AND INTERPRETATION

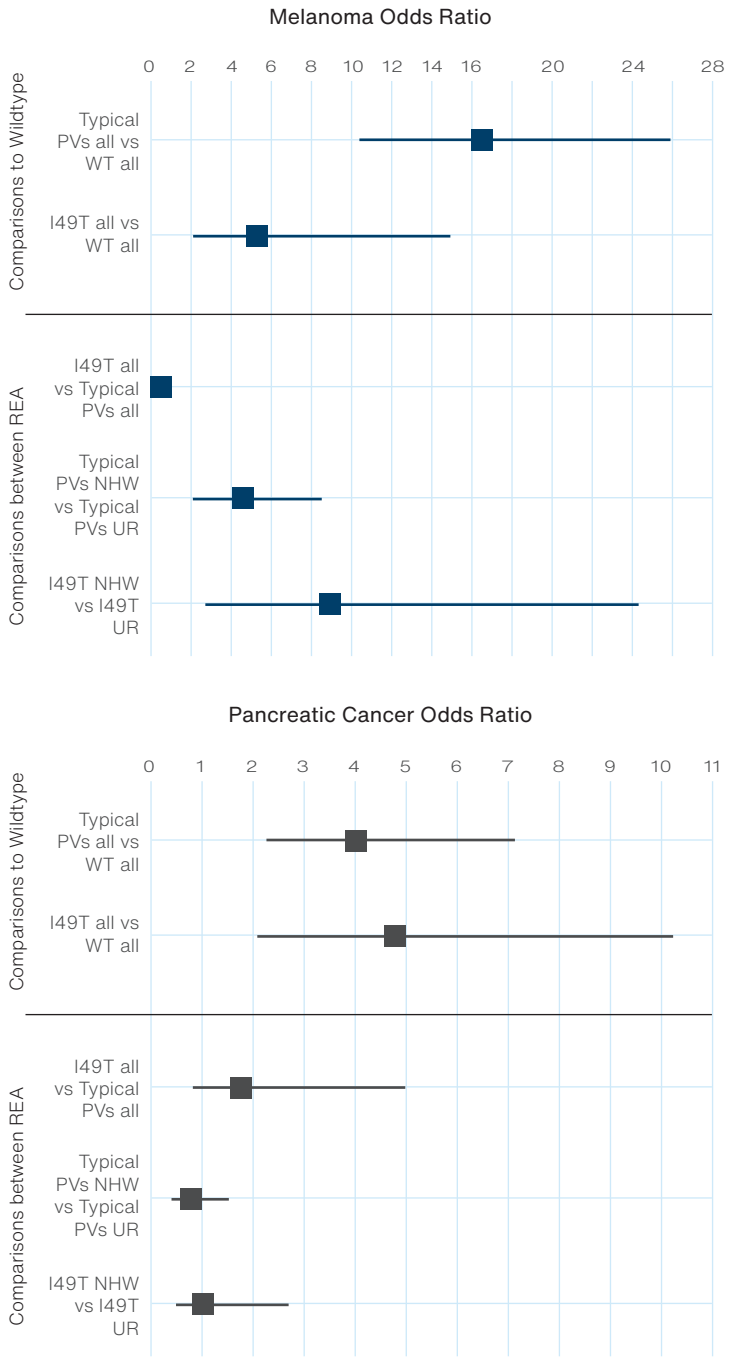
While melanoma is the classic hallmark cancer associated with *CDKN2A*, investigators found that it was significantly less prevalent in underrepresented, non-White (UR) pathogenic variant carriers. In contrast, the risk for pancreatic cancer remained significantly elevated regardless of the patient's REA group (Figure 3). Typical PVs were found to carry a much higher risk for melanoma compared to WT (OR 16.5), but when PVs were separated by REA, UR individuals had a lower risk for melanoma compared to NHW. While melanoma risks associated with p.I49T were greatly attenuated compared to typical PVs, the pancreatic cancer risks are nearly identical to typical *CDKN2A* PVs. It is likely that the lower observed melanoma rate is not driven by an biological mechanism unique to the variant itself, but is instead a result of its near-exclusive presence in Hispanic populations who have a lower baseline skin cancer incidence. Misclassifying p.I49T based on this demographically attenuated melanoma phenotype could cause substantial clinical harm by preventing patients from accessing high-risk surveillance.

WHY ANCESTRY-AWARE INTERPRETATION MATTERS

CDKN2A serves as an exemplar of how bias in data availability can reduce accuracy in variant interpretation and exacerbate healthcare disparities at the level of ascertainment, classification, and risk management. Testing criteria and interpretation frameworks that do not consider REA-specific risks may inadvertently prevent UR individuals from receiving a positive, actionable result.

Ancestry-aware variant interpretation is an essential part of the diagnostic process. By actively evaluating how REA influences clinical presentation, laboratories can provide robust, accurate, and equitable variant interpretation, ensuring that patients across all populations receive the actionable results they need to guide their medical care.

Figure 3. Melanoma and Pancreatic Cancer Odds Ratios



1. Surveillance, Epidemiology, and End Results (SEER) Program. Cancer Stat Facts: Melanoma of the Skin. National Cancer Institute. Accessed August 2025. https://seer.cancer.gov/statfacts/html/melan.html
2. Young C, et al. Assessing Melanoma and Pancreatic Cancer Risks in Diverse CDKN2A Heterozygote Populations. Genet Med. (full citation pending publication)

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MKT-ONCO-FLYR-20155-EN v1 10.07.26