

The genetic landscape of hereditary cancer in Iowa: evidence from a population geospatial analysis

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Iowa has the second highest and fastest rising cancer rate in the U.S. Approximately 10% of cancers are hereditary, and may be mitigated through high-risk screening and preventive surgery. In Iowa 3 cancers that drive high cancer rates, breast, prostate, and melanoma, are often hereditary. While environmental and behavioral factors are under study, the genetic contribution to cancer risk in Iowa remains uncharacterized. Iowa has a stable population, without rapid expansion, making it well suited for identifying regionally enriched variants.

We hypothesize that regionally enriched hereditary cancer variants contribute to Iowa's high cancer rates.

Methods: De-identified data were obtained for 17,530 patients residing in Iowa, who underwent multi-gene panel testing from January 2018-August 2025 through one of the two main diagnostic laboratories responsible for germline cancer testing in Iowa, and compared to data for 5 surrounding states. Pathogenic/likely pathogenic variants (P/LP) and VUS with ≥ 5 positive tests overall (1,758 variants across 90 genes) were analyzed by Fisher's exact test with Benjamini–Hochberg correction (FDR <10%). Variants with FDR <10% were considered significant and further characterized.

Results: Fewer than 1% of Iowans have received a hereditary cancer test despite the high cancer rates. Three P/LP variants (*CDH1* c.2165-1G>C; *MSH6* c.651dupT; *PALB2* c.3456dupA) and two VUS (*AXIN2* c.2141+4A>G; *RAD51D* c.202G>A) were found at a significantly higher rate in Iowa. *PALB2* c.3456dupA was found in 15 individuals (12 Iowa families), a rate 19.2 times higher than in surrounding states, and only in females with breast cancer, of White/unknown race, distributed across ages and the state. *CDH1* c.2165-1G>C was found 11 individuals from 9 Iowa families (23.5 times higher rate), in males and females of younger ages, of White/unknown race, and clustered in

northeastern Iowa. Two recurrent lower-risk P/LP variants in *APC* and *CHEK2* were found at a significantly lower rate in Iowa than surrounding states.

Conclusion: Iowa harbors hereditary cancer variants not commonly observed in surrounding states. Expanded genomic screening could improve identification of at-risk individuals and enable targeted prevention. Functional analysis of identified VUS may support reclassification and enable access to high-risk screening for Iowans and their families. Geospatial analysis of hereditary cancer variants is an effective mechanism to characterize regional genetic risk.

Learning Objective: Summarize the genetic landscape of hereditary cancer variants in Iowa and its implications for targeted genomic screening and prevention strategies.