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Committee Chair: Dr. Asha Bhatt
Committee Co-Chair: Dr. Winnie Henderson

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Category II

Hereditary Cancer Genetic Testing for All? A Retrospective Analysis on Genetic Mutations Found in Individuals Not Meeting NCCN® Guidelines

Jenna Cooke[1], Meghan E. Burgess[1], Heather Fecteau[2]

[1]*Midstate Radiology Associates, Connecticut, USA*
[2]*Ambry Genetics, California, USA*

Objective: Hereditary cancer genetic testing has been routinely recommended for individuals whose personal or family history meets the National Comprehensive Cancer Network® (NCCN®) guidelines. Midstate Radiology Associates (MRA) implemented universal risk screening in 2021 using the Ambry CARE Program®. This digital tool collects personal and family history, applies NCCN® guidelines, and identifies patients meeting criteria for hereditary breast, ovarian, pancreatic, prostate cancer, Lynch syndrome, and familial adenomatous polyposis. However, many individuals fall outside these guidelines or have limited knowledge of their family history. To address this gap, all patients were offered genetic testing regardless of guideline eligibility. This study analyzes four years of data from 15 MRA sites throughout Connecticut, where all were offered hereditary cancer genetic testing after risk assessment.

Materials and Methods: A retrospective analysis was conducted across MRA sites from 11/1/2021 to 10/20/2025 to evaluate patients who underwent hereditary cancer genetic testing and tested positive for a pathogenic variant. Testing was performed using Ambry Genetics' CancerNext-Expanded® Hereditary Cancer Panel, which includes 77 genes. The primary outcome was the proportion of positive cases among individuals not meeting NCCN® guidelines. Secondary analyses stratified this cohort by personal and family cancer history, age, ethnicity, and positive gene distribution.

Results: A total of 8,100 individuals underwent genetic testing; 58% (4,731) met NCCN® guidelines, and 42% (3,369) did not. Among all tested, 801 were positive for a pathogenic variant: 66% (539) met NCCN® criteria, while 34% (262) fell into the non-guideline cohort (NGC). Within the 262 NGC positives, 60 reported no personal or family cancer history; 32 had a personal cancer diagnosis (40% breast cancer, 38% non-melanoma skin cancer); and 65% (170) had family history that did not meet NCCN® criteria. The cohort was predominantly White/Caucasian (74%), with smaller representation from Hispanic/Latino (6.5%) and Black/African American (3.4%). Most pathogenic variants were found in older adults, with the highest representation in ages 60–69 (26%) and 50–59 (24%), while those under 40 accounted for only ~15%. The most frequent genetic mutation in the NGC was *MUTYH* (20%), followed by *CHEK2* (16%). Genetic mutations were also present in the following genes: *APC, ATM, BAP1, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CFTR, CHEK2, FH, FLCN, HOXB13, LZTR1, MBD4, MITF, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NTHL1, PALB2, PMS2, POT1, RAD51C, RAD51D, SDHA, SDHB, SDHD, SMAD4,* and *VHL*.

Conclusion: These findings support the potential value of expanded or universal genetic testing strategies, particularly in populations with limited family history or those outside current clinical criteria.

Keywords: Genetic testing; guidelines