

Genetic Screening of Adults for CDC Tier 1 Genomic Conditions reveals 90% of Risk Carriers are not previously identified in typical care

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Background

- CDC Tier 1 Genomic Conditions Familial Hypercholesterolemia (FH), BRCA related Hereditary Breast and Ovarian Cancer (HBOC), are highly actionable and penetrant conditions (9 genes)
- Penetrance estimates of these diseases are based on population first ascertained with disease.
- Resultantly, current testing guidelines use family history and/or demographic/ethnic background
- As a step towards preventive health, we explored the role of genetic screening, irrespective of family history or disease state to understand the clinical impact of CDCT1 conditions in the general population.

Methods

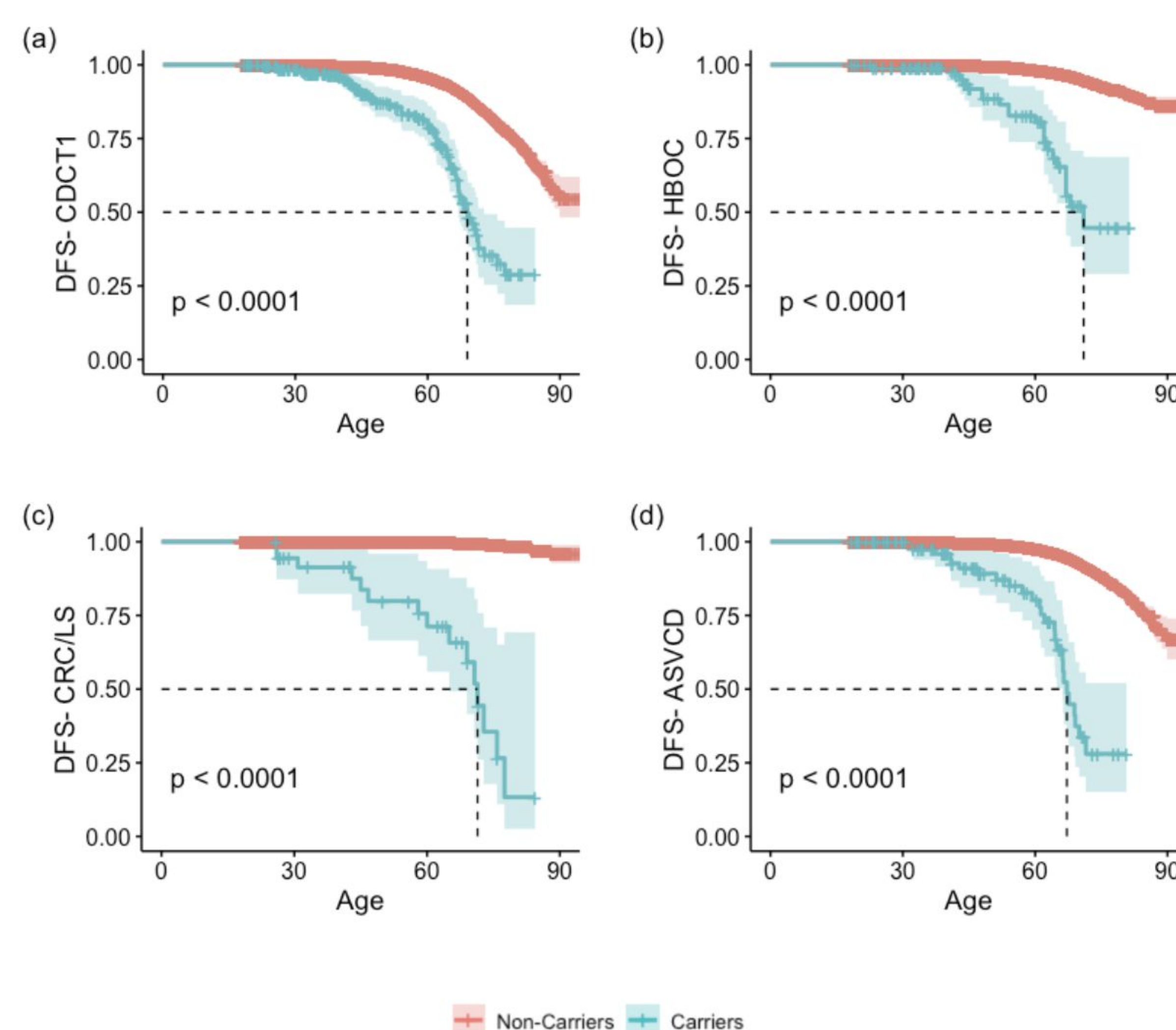
- Unselected adult volunteers (n = 23,713) underwent clinical Exome+ sequencing as a part of the Healthy Nevada Project (HNP) in Northern Nevada (Renown Health, Reno, Nevada) from March 15, 2018, to Sept. 30, 2018.
- We identified “carriers” of pathogenic/likely Pathogenic (P/LP) variants in CDC T1 genes and “non-carriers”
- We analyzed available medical records for 243 carriers and 18,955 non-carriers for diagnosis codes related to a diseases related to the underlying genetic variant and age at first diagnosis of relevant disease.

Results

- 1 in 80 were carriers of P/LP variants in 9 genes
- >90% of carriers were undetected in current medical practice, >80% had no documented family history.
- 26% of carriers had manifested disease, with a median age of first presentation at age 60, 45, and 62 for HBOC, LS, and FH.

Results

- Carriers have an approximately 30 year acceleration of disease presentation relative to non-carriers



- Disease penetrance in unselected carriers for LS and FH is not different from carriers identified from family history. Family history plays an independent role in HBOC disease manifestation

Discussion

- Average screening protocols and guidelines may not adequately identify at-risk individuals.
- Increased population screening to identify highly-penetrant disease carriers would enable earlier intervention to decrease the morbidity and mortality rate of FH, LS, and HBOC

