
First-line preventative genetic screening: Disease penetrance in Tier 1 inherited diseases in an all-comers population is similar to family history selected populations

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Clinical testing guidelines are focused on family history or demographic/ ethnic background as penetrance estimates for inherited genetic disease are often derived from populations with known disease. It is unknown if disease penetrance in unselected populations will be lower than in selected populations. Here we report on disease penetrance in three inherited autosomal dominant diseases: Familial Hypercholesterolemia (LDLR, PCSK9, APOB), Hereditary Breast and Ovarian Cancer (BRCA1, BRCA2) and Lynch Syndrome (MLH1, MSH2, MSH6, PSM2) in unselected adult volunteers (n = 23,709), who 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 more than 290 carriers of pathogenic/ likely pathogenic alleles, >80% of which have medical records. We report that over 90% of these carriers are undetected in the medical system with over 80% without any documented family history. In addition, 26% of these carriers have already manifested with disease, with a median age of first presentation of relevant disease at age 60, 45 and 62 for HBOC, LS and FH. When examined more closely, we find that disease penetrance in unselected carriers for LS and FH is not different from carriers identified from family history. 40% of unselected LS carriers present with colorectal or other cancers by age 40, similar to disease registries of LS patients. For FH, we estimate that 50% of unselected FH carriers will present with atherosclerotic related cardiovascular disease by age 60. We also find BRCA carriers have greatly elevated risk for HBOC. With ~90% of disease presentation occurs after 40, and 70% before the age of 65, our experience suggests that a population health based approach to genetic screening in younger patients can provide substantial clinical, economic, and patient benefit.