BRCA Testing in High Risk Populations

Ranjit Manchanda

Abstract

The traditional family-history (FH) based approach to genetic testing for BRCA mutations misses >50% of at risk carriers. BRCA mutations (founder mutations) are more prevalent in some populations (e.g. Ashkenazi Jews). Risk models used for this purpose are moderately affective at predicting a mutation but have poor ability/NLR at ruling out a BRCA mutation. Technological advances have raised the possibility of systematic population-based genetic testing for BRCA mutations in these populations but some uncertainty has remained on whether risks outweigh the benefits.

A randomised controlled trial (GCaPPS, ISRCTN73338115) of BRCA1/2 gene-mutation testing in the Ashkenazi-Jewish (AJ) population compares psychological/ quality-of-life consequences of Population-Screening (PS) with testing those fulfilling standard FH-based clinical criteria alone. A decision analytic model has compared cost-effectiveness of population-based BRCA testing with the standard FH-based approach in AJ women over 30 years. Model probabilities utilise GCaPPS trial/published literature to estimate total costs, effects in terms of Quality-Adjusted-Life-Years (QALYs), cancer incidence, incremental cost-effectiveness ratio (ICER) and population impact. AJ population and BRCA-test result data (from 2000-2010) obtained through ONS and all London NHS clinical genetics laboratories provide NHS BRCA detection rates. This along with BRCA prevalence estimates were used to calculate and simulate (n=10000000) time-to-detect all FH-positive BRCA-carriers in the London AJ-population (BRCA incidence=binomial distribution; rate of detection=Poisson distribution). Impact of changes in NHS funding and BRCA prevalence were assessed assuming correlations: ρ=0.25, 0.5, 0.75.

30 BRCA-carriers were identified in 1034 Ashkenazi-Jews, giving a BRCA1/2 prevalence= 2.9%(CI:1.97,4.12): BRCA1= 1.55%(CI:0.89,2.5), BRCA2= 1.35%(CI:0.74,2.26). 18/30 (60%) were FH-negative and not identified using clinical criteria. The prevalence of FH-positive/FH-negative carriers= 1.16%/1.74%. FH-based testing has a sensitivity= 40%(CI:22.7,59.4%), specificity= 88.45%(CI:86.3,90.4%), PLR= 3.46 (CI:1.95,5.34) and NLR= 0.68 (CI:0.46,0.87). There was no significant difference between FH and PS-arms at 7-days or 3-months for a range of psychological measures of anxiety, depression, health-anxiety, distress, uncertainty and quality-of-life. Overall anxiety (p=0.0001), and uncertainty (p=0.0008) associated with genetic testing decreased, but quality-of-life and health anxiety did not change with time. The BRCA detection rate in London AJ from 2006-2010 =34.2/year, with the pattern being randomly spread (Poisson-model goodness-of-fit test (p=0.439). Modelling BRCA detection rates and BRCA prevalence estimated it would take 44.8 years (CI: 21.02, 66.76) to detect all FH-positive BRCA carriers in London. Compared to FH-based testing population-screening can save 0.090 more life-years and 0.101 more QALYs resulting in 33 days gain in life-expectancy. Population-screening is cost saving with a baseline discounted ICER of -2079£/ QALY. This approach may lead to 276 fewer ovarian and 508 fewer breast cancer cases in the UK.

Compared to FH-based testing, population-based genetic testing in Ashkenazi-Jews doesn't adversely affect short term psychological/quality-of-life outcomes, detects additional BRCA carriers

and is highly cost effective. Efficient, acceptable and more cost-effective ways of delivering information on genetic risk on a population basis are also necessary for this. Telephone and DVD based approaches have been found to be cost efficient. This suggests the feasibility of a population based approach in some populations with a high BRCA prevalence. It could have significant policy implications for the AJ population (and potentially other similar populations) which can save lives, but will require a change in the current paradigm of a FH-based approach to genetic testing in such populations.