Cost-effectiveness analysis of germ-line BRCA testing in women with breast cancer and cascade testing in family members of mutation carriers

A germline mutation in the breast cancer susceptibility genes BRCA1 and BRCA2 is associated with an increased risk of breast and ovarian cancers. Women with a BRCA mutation have a 40% to 80% lifetime breast cancer risk and a 10% to 40% risk of ovarian cancer.(1-3) The prevalence of BRCA mutations varies based on a number of factors such as type of cancer, age at diagnosis, family history of cancer, and ethnicity.

Various interventions have been found to be effective in reducing the risk of cancer in BRCA mutation carriers including risk-reducing mastectomy and/or bilateral salpingo-oophorectomy.(4-6) In the presence of effective strategies to reduce the incidence of BRCA-related cancers, genetic testing has been recommended to identify carriers who would benefit from cancer prevention interventions.(7, 8) Given the high cost of the test and the potentially large number needed to test to detect a mutation, though, there has been an increasing interest in the cost-effectiveness of BRCA mutation testing to inform which genetic testing program would deliver value for money. One option is to have a population-based genetic screening whereby individuals without cancer are screened if they belong to a group with high prevalence of BRCA mutation based on ethnicity such as the Ashkenazi Jewish. Another approach is to test people who have a family history of cancer but in whom a familial mutation has not been identified. A more focused approach entails testing affected individuals (i.e., individuals diagnosed with cancer) who have disease characteristics suggesting a high probability of carrying a mutation (e.g., early onset breast cancer) to determine whether a germline BRCA mutation is present, followed by BRCA testing of the relatives (i.e., cascade testing) of those affected individuals who test positive for the mutation. The latter strategy is an efficient approach which is supported by the recent international guidelines for BRCA mutation testing.(6-9)

The Australian Medical Services Advisory Committee (MSAC) considered the genetic testing of hereditary mutations predisposing to breast and/or ovarian cancer under the clinical utility card (CUC) approach whereby individuals diagnosed with cancer who have disease characteristics suggesting a high probability of carrying a mutation (e.g., early onset breast cancer) are tested, followed by BRCA testing of the relatives of those who test positive for the mutation. However, there was no published evidence about the cost-effectiveness of this approach; and therefore, the aim of this project was to assess the cost-effectiveness of germline BRCA testing in women with breast cancer, and the cascade testing for the relevant mutation in the first- and second-degree relatives of the women who test positive for the mutation, compared with no BRCA testing.(10) The team involved in this project comprised researchers, clinicians and policy makers from different Australian institutions.

A cost-effectiveness analysis was conducted using a cohort Markov model from a health-payer perspective. The model estimated the long-term benefits and costs of testing women with breast cancer who had at least a 10% pre-test *BRCA* mutation probability, and the cascade testing of relatives of women who test positive. A novel analytic model was developed to integrate the costs and effects of three cohorts: 1) high-probability affected women: defined as women with unilateral breast cancer whose personal or family history of cancer using a mutation prediction score predicts a combined mutation carrier probability of >10%; 2) first degree family members

(i.e., siblings and children) of the affected women who test positive; and 3) second degree family members who are the children of siblings who test positive.(10) Model inputs were obtained from the best available relevant literature including clinical and epidemiological studies together with data from the Australian refined diagnosis-related groups (AR-DRG) and Australian Medicare Benefits Schedule fees. An annual discount rate of 5% was applied to outcomes and costs, and results were presented in 2016 Australian dollars (AU$).

Compared with no testing, BRCA testing of affected women resulted in an incremental cost per quality-adjusted life-year (QALY) gained of AU$18,900 (incremental cost AU$1,880; incremental QALY gain 0.10) with reductions of 0.04 breast and 0.01 ovarian cancer events. Testing affected women and cascade testing of family members resulted in an incremental cost per QALY gained of AU$9,500 compared with testing affected women only (incremental cost AU$665; incremental QALY gain 0.07) with additional reductions of 0.06 breast and 0.01 ovarian cancer events. The model predicted that cumulative risks by age of 70 years for *BRCA* carriers was 53% for breast cancer, 25% for ovarian cancer, and 59% for contralateral breast cancer. With *BRCA* testing, the corresponding risks were 24% for breast cancer, 19% for ovarian cancer, and 28% for contralateral breast cancer. These results were stable over a range of plausible estimates for the input parameters. In a probabilistic sensitivity analysis, the probability of *BRCA* testing being cost-effective was 85% for testing affected women only and 90% for testing affected women followed by cascade testing of family members of mutation carriers.(10)

The integrated model used allowed the estimation of the downstream costs and benefits of testing family members who wish to be tested to prevent future cancers. Although testing family members would result in additional costs, the benefits of testing and risk-reducing surgery would offset the additional costs of genetic testing. Thus, the overall conclusion was that BRCA testing in women with breast cancer is cost-effective and is associated with reduced risk of cancer and improved survival; however, extending testing to cover family members of affected women who test positive improves cost-effectiveness beyond restricting testing to affected women only.

As a direct result of this project, women at high risk of developing breast and ovarian cancer will be offered free genetic testing, as the test is now listed on the Medicare Benefits Schedule http://www.abc.net.au/news/2017-10-12/breast-and-ovarian-cancer-test-free-for-high-risk-patients/9040274. The full paper was published in Nature Genetics in Medicine can be accessed at http://rdcu.be/D3SV

1. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. American journal of human genetics. 2003;72(5):1117-30.
2. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(11):1329-33.
3. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. Journal of the National Cancer Institute. 2013;105(11):812-22.
4. Ludwig KK, Neuner J, Butler A, Geurts JL, Kong AL. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. American journal of surgery. 2016;212(4):660-9.
5. Li X, You R, Wang X, Liu C, Xu Z, Zhou J, et al. Effectiveness of Prophylactic Surgeries in BRCA1 or BRCA2 Mutation Carriers: A Meta-analysis and Systematic Review. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016;22(15):3971-81.
6. Cancer Institute NSW. eviQ. An online service of the Cancer Institute NSW 2017 [Available from: https://www.eviq.org.au/.
7. Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27(suppl 5):v103-v10.
8. National Comprehensive Cancer Network (NCCN). Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Clinical Practice Guidelines in Oncology [Internet]. January 2017. Available from: https://www.asco.org/sites/new-www.asco.org/files/content-files/research-and-progress/documents/nccn-guideline-genetics-screening-breast-ovarian.pdf.
9. National Institute for Health and Care Excellence. Clinicalguideline164-familial breastcancer. 2015.
10. Tuffaha HW, Mitchell A, Ward RL, Connelly L, Butler JRG, Norris S, et al. Cost-effectiveness analysis of germ-line BRCA testing in women with breast cancer and cascade testing in family members of mutation carriers. Genetics in medicine : official journal of the American College of Medical Genetics. 2018;20(9):985-94.