Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The objective was to determine the level of risk at which it becomes cost-effective to test women for mutations in breast cancer 1 or 2 (BRCA1/2) genes, which indicate breast cancer susceptibility. If the knowledge of mutation improved a woman's utility by at least 0.006, then testing was cost-effective regardless of the pre-test risk level. Despite the good methods, a lack of detailed reporting around the model inputs makes it difficult to assess whether the authors’ conclusions are robust.

Type of economic evaluation
Cost-utility analysis

Study objective
The objective was to determine the level of risk at which it becomes cost-effective to test women for mutations, which indicate breast cancer susceptibility, in breast cancer 1 or 2 (BRCA1/2) genes. Testing was compared with no testing.

Interventions
The test strategy was a test for BRCA1/2 gene mutation at age 35 years, followed by the offer of preventive surgery if a mutation was found. Preventive surgery was either an oophorectomy or a mastectomy and screening continued according to the recommendations at the time. The no-test strategy was screening according to recommendations only.

Location/setting
USA/primary care.

Methods
Analytical approach:
A semi-Markov model was developed to estimate the costs and health outcomes of testing or not testing for women aged 35 years, who had a family risk of breast or ovarian cancer or who were concerned about having the mutation. In the base-case, women entered the model with an estimated pre-test probability of having a genetic mutation of 10% or more. The time horizon of the model was lifetime (up to 70 years from testing). The authors stated that the analysis was conducted from the societal perspective, with a boundary of the patient-specific costs and benefits only.

Effectiveness data:
The effectiveness data for the sensitivity and specificity of genetic testing were from published studies (Nelson, et al. 2005 and Walsh, et al. 2006, see ‘Other Publications of Related Interest’ below for bibliographic details). Another published study provided the reduction in risk due to preventive surgery. The key clinical parameters included: breast or ovarian cancer incidence rates; transition probabilities between health states (well, breast cancer, ovarian cancer, death), based on test results and preventive surgery; the sensitivity and specificity of testing; and the rates of uptake of preventive surgery.

Monetary benefit and utility valuations:
The majority of the utilities were from the published literature, where the time trade-off approach was used to estimate the utilities for breast or ovarian cancer and preventive surgeries in women aged 33 to 50 years (Grann, et al. 1999, see ‘Other Publications of Related Interest’ below for bibliographic details). The utility estimates for breast cancer were informed by four additional studies. The disutility for cancer diagnosis was based on the Cost-Effectiveness Analysis (CEA) Registry. These data were supplemented by the authors’ judgements to estimate the one-time increase in utility...
due to receiving a negative result, as well as the linear increase in utility from the year of diagnosis.

Measure of benefit:
The benefit measure was quality-adjusted life-years (QALYs), which were discounted at an annual rate of 3%.

Cost data:
The cost categories were those of health care and out-of-pocket patient expenses. These included the costs of genetic testing and counselling, costs when well, terminal care costs, costs for cancer treatment, and preventive surgery costs. All costs were from published sources including Kaiser Permanente, Medicare, and Drug Topics' Red Book. The price year was 2006 and older costs were inflated to 2006 US dollars ($) using the medical care component of the Consumer Price Index. An annual discount rate of 3% was applied.

Analysis of uncertainty:
Sensitivity analysis was performed to determine the threshold probability of mutation that makes genetic testing cost-effective. One-way sensitivity analysis was performed to discover the most sensitive parameters by varying all the model inputs across a range of values. Scenario analyses explored the possibility of including inconclusive test results in extreme cases. A probabilistic sensitivity analysis, using 10,000 Monte Carlo simulations, was performed and the results were presented using a confidence ellipse and a cost-effectiveness acceptability curve.

Results
In the base case, assuming the guideline level of mutation, the test strategy was estimated to cost $118,000 and result in 22.9 QALYs. The no-test strategy was estimated to cost $117,000 and result in 22.7 QALYs. The incremental cost-effectiveness ratio (ICER) for testing over no testing was $9,000 per QALY.

The sensitivity analysis showed that the test strategy was cost-effective at a pre-test probability of mutation of 0% if the increase in utility (or utility gain) from a negative test was at least 0.006; in this case the ICER over no testing was $25,400 per QALY.

One-way sensitivity analyses showed that the results were most sensitive to the utility following BRCA1/2 gene mutation diagnosis in the first year, the utility during the first year after mastectomy, the utility gain from a negative result, and the discount rate.

Scenario analyses including inconclusive tests, which were excluded in the base case, resulted in not testing being dominant (more effective and less costly than testing) when all test results were either false-positive or false-negative.

The probabilistic sensitivity analysis showed that there was a 70% probability of testing being cost-effective or dominant compared with not testing at a willingness-to-pay of $50,000 per QALY.

Authors' conclusions
The authors concluded that genetic testing for BRCA1/2 was cost-effective regardless of pre-test probability of mutation, as long as the knowledge of the BRCA1/2 mutation status improved a woman's utility by at least 0.006. They suggested that it was appropriate for insurance plans to cover BRCA1/2 testing even for women with a relatively low pre-test probability of mutation. They also noted that further research into the frequency of inconclusive results was needed, given its significant impact on the cost-effectiveness results and the increasing use of magnetic resonance imaging as part of cancer surveillance.

CRD commentary
Interventions:
The interventions were relevant in the authors’ setting since the analysis compared a test strategy against not testing, which was the practice at the time. The clinical pathways were well described, but the genetic testing techniques were not discussed.

Effectiveness/benefits:
It was evident that several sources were used to populate the model, but a systematic review of the literature was not
reported and it is not possible to determine if the best available evidence was used. The sensitivity and specificity estimates appeared to be based on good studies, but only limited details were provided and no quality assessment was undertaken. The utility estimates were satisfactorily reported and based on a number of potentially good sources. These were augmented by the authors’ professional judgements, which were appropriately tested in sensitivity analyses. Only limited details of the primary studies were given. The authors reported that the time trade-off method was used to derive the utilities, but they provided no details of whose preferences were measured.

Costs:
The perspective was stated to be societal, but it is not clear that this was correct. A previous study had shown that breast cancer did not significantly affect a woman’s wages, which could justify the exclusion of productivity losses, but only the benefits and costs incurred by the patient were evaluated and so many of the costs that you would expect to see evaluated from a societal perspective were not considered. The cost estimates were well reported and came from what appear to have been relevant and reliable sources. The price year, inflation using the medical care component of the Consumer Price Index, and discounting were all appropriately reported.

Analysis and results:
The analytical approach was well reported and the semi-Markov model used to estimate the costs and effects from both strategies was valid. The results were reported clearly and in full. The issue of uncertainty was addressed through univariate sensitivity analyses and probabilistic sensitivity analysis and a confidence ellipse and cost-effectiveness acceptability curve were presented. The sensitivity analysis results for the sensitivity and specificity of testing were not reported (see note). The authors highlighted the impact of inconclusive results on the cost-effectiveness and the fact that cancer and preventive surgery utilities might now be higher since the estimates were based on studies published between 1999 and 2005.

Note: after this abstract was published the following additional information was provided by the authors.

”Due to space limitations, we reported the value ranges used for all variables included in the sensitivity analysis, but detailed sensitivity results were reported only for the four variables to which the model was most sensitive. Therefore, although the sensitivity of the model to the sensitivity and specificity of testing was not directly reported, it was implied that the model was less sensitive to those than to the variables discussed on page 212 of the paper. In addition, sensitivity and specificity variation was included in the probabilistic sensitivity model.”

Concluding remarks:
The methods were satisfactory, but the lack of reporting of a literature review and the analysis of the sensitivity and specificity of genetic testing, makes it difficult to assess whether the authors' conclusions are robust. Given the impact of considering inconclusive results on the cost-effectiveness, the authors' conclusions should be considered with caution.

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