Genetic counselling for hereditary predisposition to ovarian and breast cancer

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Since the identification of BRCA 1 and 2 in 1995, testing for mutations in these genes has been offered to cancer patients and their families by clinical genetics services. These services are provided across Europe by a small number of health professionals, and are therefore low volume, and low capacity and patients experience considerable delays, both in seeing a clinician and in laboratory testing. The UK private sector, driven by consumer demand and professional competition, has significantly reduced these delays. The development of a new class of therapeutic agent, the PARP inhibitors, is likely to drive the BRCA testing services towards the UK private sector model with much faster turnaround times. Several new genetic tests are now available including CYP 2D6 genotype analysis and the BCtect test. The clinical interpretation of these tests is complex, and the professional community has been naturally cautious about adopting new tests in clinical care. This article will examine the consequences of expected changes in BRCA testing practice, and consider the positioning of new tests in the patient pathway, and the messages given by health professionals.

Key words: BCtect, BRCA1/2 testing, clinical service development, CYP 2D6 genotyping, PARP inhibitors, tamoxifen

background

Traditionally BRCA testing services have been provided by clinical genetics health professionals working in teams according to well-established protocols, which are similar across different European countries. ESMO has been involved in disseminating information on current clinical practice, and in standardizing practice across Europe. The small number of health professionals involved in providing clinical genetic services has resulted in patients experiencing considerable delays in accessing the appropriate professional opinion and in receiving a result from the genetic testing laboratory, with a combined delay of 4–5 months being accepted as the norm.

In the UK private sector, with the drivers of consumer demand and professional competition, most referred patients are offered an outpatient appointment within 1 week. A commercial organization, Lab21, offers complete BRCA1 and 2 sequencing within 21 working days maximum as routine, and will offer a 10-working-day turnaround at a higher price if required.

epidemiological evidence supporting cancer risk analysis in BRCA1/2 carriers

It has been estimated that 3%–5% of breast cancers are caused by a dominantly inherited mutation. A strong family history of breast and/or ovarian cancer has long been recognized as a risk factor and is in some cases indicative of a germline mutation. However, male carriers, premature death and unconfirmed diagnoses in a pedigree can all complicate the identification of individuals at high risk. Guidelines commonly place women in one of three risk categories—low, moderate or high [1]; and further referral for genetic or clinical screening procedures will depend on such classifications.

The BRCA loci were identified by linkage two decades ago and further analysis has shown that mutations in BRCA1 and BRCA2 together account for ~85% of families with four or more cases of breast cancer [2]. The results suggest that a number of other low penetrance genes may also be of importance. Since the BRCA genes are large, and mutations both numerous and widespread, identification of the genetic lesion is not always straightforward. Individuals from certain founder populations, such as those of Ashkenazi Jewish descent, commonly carry one of a small number of mutations, which can therefore facilitate carrier identification. Estimates of risk in BRCA1/2 carriers have varied, often confounded by ascertainment. A meta-analysis of 22 studies by Antoniou and colleagues [3] found cumulative risk of breast cancer by age 70 in BRCA1 and BRCA2 carriers to be 65% and 45%, respectively. Risk of ovarian cancer by age 70 was 39% (BRCA1) and 11% (BRCA2). However, due to allelic heterogeneity, the actual risk conferred by a particular mutation is likely to diverge from these estimates. The ‘ovarian cancer cluster region’ in BRCA2 is illustrative of such allelic heterogeneity, conferring
increased risk to ovarian cancer but reduced risk to breast cancer [4] (Figure 1).

**BRCA1/2 testing in clinical practice**

A family considered to be at high risk within the current guidelines [1] will be offered genetic testing after consultation with a member of the UK National Health Service (NHS) clinical genetics team. In most circumstances it is usual to first offer testing to a family member who has had either breast or ovarian cancer, and once a mutation has been identified in her, offer testing to other unaffected members of the family, after further discussion [5]. This two-step process is considered good clinical practice, but is not always essential. It is possible, for example to offer testing to an unaffected Ashkenazi woman without knowing whether there is a mutation present in an affected family member. The clinical implications of a positive test are relatively clear, and that unaffected individual is at significant risk of developing breast and/or ovarian cancer in their lifetime. The clinical implications of a negative test in these circumstances are much less clear, and most clinicians would advise the unaffected individual to continue with regular screening. There are many families that are seen in the clinic whose family history is not quite strong enough to meet current criteria for high risk, and these individuals may be offered regular screening within a clinical trial [6], but in general will not be offered genetic testing. Different clinical services may use slightly different criteria for classification, but there is broad general agreement. Little research has been done on the experiences and possible anxieties of individuals not offered testing within the NHS, who may feel they are being deprived of services because of rationing.

In the UK private sector, it is customary to give information to patients and their relatives as outlined above, but ultimately the decision to proceed with testing will be taken by the patient. In general most private medical insurers will not pay for BRCA1/2 testing, so the patient will have to fund the test from their own resources. Currently Lab 21 will offer BRCA1/2 testing to patients who have been seen by a consultant cancer geneticist, and who have signed a consent form [7]. Arrangements regarding the information given as part of the informed consent process remain the responsibility of the physician ordering the test who has to declare that consent has been obtained. These arrangements are similar in the USA where Myriad Genetics Inc. offers BRCA1/2 testing [8].

A careful analysis of the family history may in some circumstances yield enough clinical information to facilitate management decisions, and genetic testing does not add much. For example in the family shown (Figure 2), the 38-year-old breast cancer patient has a strong family history of breast and ovarian cancer. She has a significantly increased lifetime risk of ovarian cancer, and has a significantly increased risk of a new second breast cancer in the other breast on the basis of her family history and personal history. Identifying a mutation in BRCA1 or 2 in her may yield slightly more definitive risk information, but is unlikely to significantly change the management options available to her.

**the development of a new therapeutic drug class that targets tumours in BRCA1/2 mutation carriers**

BRCA2 has been reported to act as a tumour suppressor by interacting with the RAD51 protein during homologous recombination, which is a process that repairs DNA lesions in the cell in an error-free manner [9]. Deficiency in BRCA2 leads to the cell using alternative mechanisms for DNA repair such as non-homologous end joining [9]. The normal cells in BRCA2 carriers carry one copy of the normal gene and one copy of the mutated BRCA2 gene, as shown in Figure 3.

When a tumour develops in a BRCA2 carrier, then the tumour cells lose the normal copy of the gene and only carry the mutated copy, and therefore these cells are effectively BRCA2 deficient, as shown in Figure 4.

This two-stage model of tumorigenesis in breast cancer is simplistic, and the reality is illustrated in Figure 5, with multiple events including loss of tumour suppressor genes eventually leading to the malignant phenotype.

One of the important components of the alternative repair mechanisms used in BRCA2-deficient cells is the poly ADP-ribose polymerase (PARP) family [10]. Several drugs have now been developed that inhibit various members of the PARP family, known as PARP inhibitors [11]. These drugs have been shown to inhibit the growth of BRCA2-deficient mammary tumour cells lines in vitro [12]. They inhibit growth of BRCA2-deficient xenografts in mice, and when given in combination with carboplatin, the time to tumour relapse and death was

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**Figure 1.** (A) Cumulative risk of breast (diamonds) and ovarian (squares) cancer in BRCA1 mutation carriers. (B) Cumulative risk of breast (diamonds) and ovarian (squares) cancer in BRCA2 mutation carriers. Both diagrams from Antoniou et al. 2003 [3]
significantly increased in these mice [13]. Early clinical trials in BRCA carriers with cancer have been promising and several large phase III trials are now in progress [14]. These PARP inhibitors appear to be particularly effective in the tumours of patients who lack one component of the homologous recombination pathway [15], and so BRCA1 and 2 carriers become an obvious, easily identifiable target group, although it is likely that other target groups will be identified with time. 

**implications of this development for traditional clinical practice in BRCA1/2 testing**

The available preclinical and clinical evidence suggests that PARP inhibitors are particularly effective in BRCA gene carriers, and therefore there is now a therapeutic driver to the development of a speedy and effective BRCA testing service. The current UK NHS model of service delivery, with significant delays as outlined above, will not be acceptable, and it will become essential to identify speedily BRCA gene carriers amongst the breast and ovarian cancer population. The reliance on family history to gate-keep those offered testing may well become redundant, and widespread testing is likely to become common across Europe. However, the identification of a BRCA mutation in a cancer patient has important clinical implications for unaffected members of that patient’s family, and these members will require access to accurate and understandable information before they consider testing. The development and introduction into clinical practice of the PARP inhibitors will drive a much closer integration between traditional genetic testing services and oncology treatment services. It is likely that different countries across Europe will develop different models of service delivery, and ESMO has a central role to play in these developments.

**the identification of low-penetrance genes predisposing to inherited breast and ovarian cancer**

Mutations in BRCA1/2 explain only a proportion of the increased risk seen in families exhibiting aggregation of breast and/or ovarian cancer. Linkage studies have been largely unsuccessful in identifying additional susceptibility loci suggesting that remaining variance in predisposition is likely due to a large number of low-penetrance variants. Over the past decade genome-wide association studies have attempted to identify polymorphisms predisposing to breast and ovarian cancer with some success.

Variants at DNA repair loci (CHEK2, ATM, BRIP1 and PALB2) have been shown to be associated with increased risk of breast cancer although the variants are rare and therefore explain only a small proportion of the remaining predisposition. A three-stage association study by Easton and colleagues [16] identified five novel breast cancer susceptibility loci. The most significant association was with a single nucleotide polymorphism found in FGR2 (encoding fibroblast growth factor receptor 2) although identification of the causal variant was unsuccessful. It was estimated that the five loci together explain 3.6% of the increased risk seen in multi-case families.

Further work by Mavaddat et al. [17] has suggested that the detection of breast cancer susceptibility loci may be facilitated by restriction of the analysis by cancer subtype due to the heterogeneous nature of the disease. Whilst none of the variants studied reached a genome-wide significance level, association of variants at the subtype level was masked when looking at overall effect.

**analysis of inherited genotype may provide information to help guide choice of adjuvant therapy in breast cancer**

Tamoxifen has been a standard, effective adjuvant treatment of both pre- and postmenopausal breast cancer for over two decades but a significant number of patients relapse. Clinical outcome with adjuvant tamoxifen therapy may be influenced by inherited variation in drug-metabolizing enzymes providing
a possible mechanism for disease recurrence. The metabolic conversion of tamoxifen to the potent antiestrogen endoxifen, which targets the estrogen receptor for degradation [18], relies heavily on CYP2D6. The CYP2D6 locus is extremely polymorphic resulting in four phenotypic manifestations: ultra-rapid metabolizers (functional allele duplication), extensive metabolizers (EMs) (normal activity), intermediate metabolizers (IMs) (reduced activity) and poor metabolizers (PMs) (no activity). Evidence suggests that PMs and IMs produce lower levels of endoxifen [19, 20]. The prevalence of alleles varies between populations but estimates of the poor metabolizer phenotype amongst Caucasians are typically in the region of 10%.

Alleles encoding decreased or absent function have been shown to be associated with a non-favourable outcome of adjuvant tamoxifen treatment [21, 22] and thus genotype provides useful information to guide choice of adjuvant therapy. In a recent paper [21], Schroth and colleagues demonstrated that both the PM and IM phenotype conferred increased risk of recurrence in their study population of 1325 women. The recurrence rates at 9 years of follow-up were 14.9% (EM), 20.9% (hetEM/IM) and 29.0% (PM). Cox proportional hazard modelling resulted in adjusted hazard ratios for time to recurrence of 1.90 [95% confidence interval (CI) 1.10–3.28; \( P = 0.02 \)] in the PM patients compared with EM and 1.40 (95% CI 1.04–1.90; \( P = 0.03 \)) for the hetEM/IM patients.

In addition to inherited variation in CYP2D6, environmental inhibition of the enzyme occurs with co-prescription of some selective serotonin reuptake inhibitor antidepressants. Co-prescription of paroxetine in particular, which irreversibly inhibits CYP2D6, was recently shown to be associated with increased breast cancer mortality supporting the functional importance of CYP2D6 in adjuvant tamoxifen treatment [23]. This significant association was further validated by finding a link between duration of co-prescription and mortality.

With the increasingly widespread use of aromatase inhibitors in the post-menopausal majority, both as a monotherapy and in combination with tamoxifen, genotype may provide information to guide better-informed choice of adjuvant treatment. It has been suggested that the efficacy of tamoxifen may have been underestimated in the randomized controlled trials by the inclusion of CYP2D6 PMs and IMs in the tamoxifen cohorts.

an innovative blood test providing improved detection of early breast cancer

A report outlining the development of a test using gene expression profiling of peripheral blood for the early detection of breast cancer has been recently published [24]. The authors report a prediction accuracy of 79.5%, with a sensitivity of 80.6% and a specificity of 78.3%. Details from a larger case–control series have been released by Diagenic ASA, with a reported accuracy, sensitivity and specificity shown in Table 1.

This blood test, CE marked as BCtect®, is now available in the UK private sector, and is currently under review by the National Institute of Health and Clinical Excellence (NICE) for possible use within the NHS. The first meeting of the BCtect® UK strategy group agreed a conservative positioning of the test as outlined in Figure 6.

Table 1. Results reported by Diagenic ASA of case–control studies supporting the CE marking of BCtect®

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<th>Validation (N = 109)</th>
<th>Calibration (N = 223)</th>
<th>Combined (N = 332)</th>
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<td>Specificity (%)</td>
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The introduction of this test into the UK has attracted considerable press interest, with articles in several national papers [25–27]. High risk women and BRCA mutation carriers may get access to annual magnetic resonance imaging breast screening through the NHS or may consider prophylactic mastectomy. However, women with a less strong family history may remain equally concerned but are only offered annual mammography by the NHS. These women are often younger than those offered screening within the National Screening Programme, and tend to have denser breasts on mammography, with reduced detection sensitivity. A large study on annual mammography in young women with a family history of breast cancer [6] is due to issue preliminary results shortly. Early experience with the introduction of BCtect® into
private sector clinical care suggests that women who are concerned about their breast cancer risk, and do not have great faith in mammographic screening, welcome this test, and are willing to pay for it themselves. The test will become available throughout Europe by the end of 2010 [28].

disclosures

Dr James Mackay is a consultant to Diagenic ASA, and has no financial interest in, or arrangements with, a competing company.

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