The publicity surrounding the decision by Angelina Jolie to discuss her family history of breast and ovarian cancer, and the prophylactic surgery she had performed, has raised public awareness of the clinical utility of testing for the BRCA genes.1 However, several misconceptions persist, particularly regarding men's health and the role of male BRCA carriers.

In this article, the traditional service model of BRCA testing is described. Several recent developments in clinical practice are then examined, including the testing of unaffected female family relatives, and the testing of both affected and unaffected male family relatives. Finally, an innovative new product is described, which examines the activity of several genetic sequences in a prostate cancer tissue sample and gives extra information on how aggressive that
prostate cancer is likely to be, based on the gene activity pattern identified.

TRADITIONAL MODEL OF A BRCA TESTING SERVICE

Figure 1 illustrates an index patient who came to the cancer genetics clinic with a strong family history of breast and ovarian cancer. The important clinical messages to get over to the index patient are:

- It is quite likely that there is a faulty gene causing breast and ovarian cancer in this family
- If there is such a gene, the patient’s mother carries one good copy and one faulty copy of the gene
- She passes one copy on to her daughter, so even if there is a faulty gene in the family, the index patient has a 50 per cent chance of inheriting the good copy from her mother
- If she inherits the good copy, she may still develop non-genetic (sporadic) breast or ovarian cancer
- She has a 50 per cent chance of inheriting the faulty copy, which means her risk of developing genetic breast or ovarian cancer is increased but it is not inevitable that she will develop one of these cancers
- Some carriers of a faulty gene do not develop cancer, but their risk is increased
- Genetic testing, examining the BRCA1 and BRCA2 genes, is possible.

Both BRCA1 and BRCA2 are long genes, and a faulty gene is caused by a subtle spelling mistake anywhere along the sequence. Testing is traditionally a two-step process; in the first step a blood sample is taken from someone in the family who has had either breast or ovarian cancer, and the complete sequence of their BRCA1 and BRCA2 genes is examined. Only if a spelling mistake is identified can we move on to the second step and offer testing to other family members. In the second step we examine only the specific faulty letter identified in the first step, which will tell us whether that unaffected individual has inherited the good copy or the faulty copy. By following this traditional process, the quality of the clinical information that we can give an unaffected individual in a family is high. If she has inherited the good copy, her risk of developing breast or ovarian cancer is low, and if she has inherited the faulty copy, her risk of developing breast and/or ovarian cancer is high.

In some populations, including the Ashkenazi Jewish population, we do not need to do a complete analysis of the BRCA1/2 genes in step 1, as there are a small number of founder mutations, which occur at a much higher population frequency. In the Jewish population, there are three founder mutations, and so they can be offered the Multisite 3 BRACAnalysis, which looks only for the three founder mutations rather than examining the entire sequence of both genes. If a mutation is identified in an affected person, we can move on to step 2 as above, and look only for the mutation that has been identified in the family. In practice, however, we often look for the three Jewish mutations in unaffected individuals as well, just in case there are different mutations coming down either side of the family. Again, it is important that this option is discussed with unaffected patients who wish to be tested.

When a complete BRCA sequence is performed, three possible results are produced by the laboratory:

- The entire sequence of both genes has been examined and is normal
- Both genes have been examined and a known, functionally important fault has been identified – a pathogenic mutation
- A variant in the sequence of BRCA1 or BRCA2 has been identified, but it is not known if it is functionally important or not – reported as a variant of unknown significance.

RECENT DEVELOPMENTS

If a variant of unknown significance is identified, it is important to obtain as much information as possible about that particular variant, and Myriad Genetics have published the sophisticated criteria they use to categorise each variant into:
known pathogenic mutation
probable pathogenic mutation
significance unknown
probable benign variant with no clinical significance
definite benign variant with no clinical significance.

The ability to categorise these variants accurately depends on high volume testing, and the Myriad database currently holds information on more than 1 million BRCA analyses.

If we consider the unaffected relative in Figure 2, testing by the traditional method is not possible. However, technically it is possible to test the unaffected relative directly. It is important to ensure that she has been given accurate understandable information on the advantages and disadvantages of testing, but if she wishes to pay for a BRCA test privately, it is possible to offer testing. If she is found to carry a pathogenic mutation, she is at high risk of developing breast and ovarian cancer. If she is found to carry two normal BRCA1/2 genes, the clinical significance of that information is much less clear-cut than in the traditional model, and she would be considered to remain at increased risk because of her family history. In some European countries, testing unaffected relatives without first testing an affected family member is illegal and considered unethical.

ROLE OF MALE BRCA CARRIERS

Turning now to aspects of male health, consider the pedigree in Figure 4. A BRCA1 mutation has been identified in an affected female relative, so this male index patient has a 50 per cent chance of inheriting the mutation from his mother. After being given the relevant information, he may well consider being tested for that specific mutation. If he has inherited the good copy and then he has daughters, there is no need to offer testing to his daughters. If he has inherited the faulty copy, each of his daughters is at 50 per cent risk of inheriting a mutation and they may well wish testing at some stage when they are older.

A man with a BRCA2 mutation has an 8.6-fold increased risk of developing prostate cancer himself, while a man who has inherited a BRCA1 mutation has a 3.4-fold increased risk of inheriting a mutation and they may well wish testing at some stage when they are older. A man with a BRCA2 mutation has an 8.6-fold increased risk of developing prostate cancer himself, while a man who has inherited a BRCA1 mutation has a 3.4-fold increased risk of developing prostate cancer. Male BRCA carriers will often be offered a prostate cancer screening regimen, although there seems to be no standardised regimen at the moment.
of breast and ovarian cancer, but all affected female relatives are dead. It would seem entirely reasonable to offer him a Comprehensive BRACAnalysis; if a pathogenic mutation is identified in him, some of his unaffected female relatives may wish to be tested. It is important to take an accurate family history from young prostate cancer patients, concentrating on breast and ovarian cancer in female relatives, and equally important to take an accurate family history from breast and ovarian cancer patients, concentrating on young prostate cancer in male relatives. Current guidelines emphasise aggressive prostate cancer, but in our experience most relatives do not know whether or not male relatives had an aggressive cancer, but they do know the age at which the prostate cancer was diagnosed, so we prefer the concept of young prostate cancer rather than aggressive prostate cancer.

In prostate cancer cases, unselected for family history, BRCA1 mutations are present in 1.2 per cent of cases, and BRCA2 mutations are present in 0.44 per cent of cases, but the mutation pick-up rate goes up significantly if an accurate family history is taken and testing offered to those with a significant breast/ovarian family history, as illustrated in Figure 5.4

**CELL CYCLE PROGRESSION TEST**

A recent study reported that BRCA2 carriers develop more aggressive prostate cancer with shorter disease-free intervals and higher mortality.4 This report links in well with the recent release of a new test, which examines activity of 46 genetic sequences in the prostate cancer tissue, and clearly differentiates between those with a low risk of early disease progression and a high risk of early disease progression.5-8

The Prolaris test, developed by Myriad Genetics, is a risk-stratification tool, which can enable a physician to define a treatment/monitoring strategy for patients with prostate cancer, enhancing their quality of life without jeopardising their life expectancy.
Prolaris provides a quantitative measure of the RNA expression levels of multiple genes related to the progression of tumour cell division. The 46-gene expression signature includes cell cycle progression genes selected based upon correlation with prostate tumour cell proliferation: low gene expression is associated with a low risk of disease progression and high gene expression is associated with disease progression.

Prolaris can identify low- or intermediate-risk patients who may be candidates for surveillance, as well as patients who may be potentially at higher risk and who would benefit from closer monitoring or additional therapy.

The Prolaris test is being offered to selected patients by several centres in the UK private sector, with the expectation that it will improve clinical care. However, unravelling the intriguing links between inherited BRCA mutations and the aggression of the prostate cancer as defined by the Prolaris test will require further clinical research.

Clearly, from the information above, all prostate cancer is not the same. There are other resources available, in addition to genetic testing, that are useful in the fight against prostate cancer.

Declaration of interests
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REFERENCES