Introducing inherited cancer gene panel testing into clinical cancer care

Dr James Mackay, MA, MD, FRCP, FRCPE,
Consultant Genetic Oncologist,
The London Breast Clinic and University College London.

Correspondence address:
Wolfson House
UCL Department of GEE
2-10 Stephenson Way
London
NW1 4 HE

Statement of conflicting interest:
Dr James Mackay is Clinical Advisor to Myriad Genetics GmbH.

The recent major improvements in laboratory technology and expertise have made high volume genetic sequencing faster and cheaper. Rather than sequencing single genes one at a time we are now able to sequence many genes on a single sample within a reasonable time frame through the use of inherited cancer gene panel tests. Various cancer panel tests have been introduced into clinical care, in this article we will consider the important clinical issues underpinning the introduction of such tests.

Traditional model of a BRCA testing service

March 2014 marked the 20th anniversary of the identification and cloning of BRCA1 and the recognition of its role in Hereditary Breast and Ovarian Cancer syndrome (HBOC) [1]. 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 in this sample can we move on to the second step and offer testing to other unaffected family members. In the second step we only examine the specific faulty letter identified in the first step, which will tell us whether the unaffected individual has inherited the good copy or the faulty copy. By following this traditional process the quality of the clinical information which 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 inherits the faulty copy her risk of developing breast and/or ovarian cancer is high.

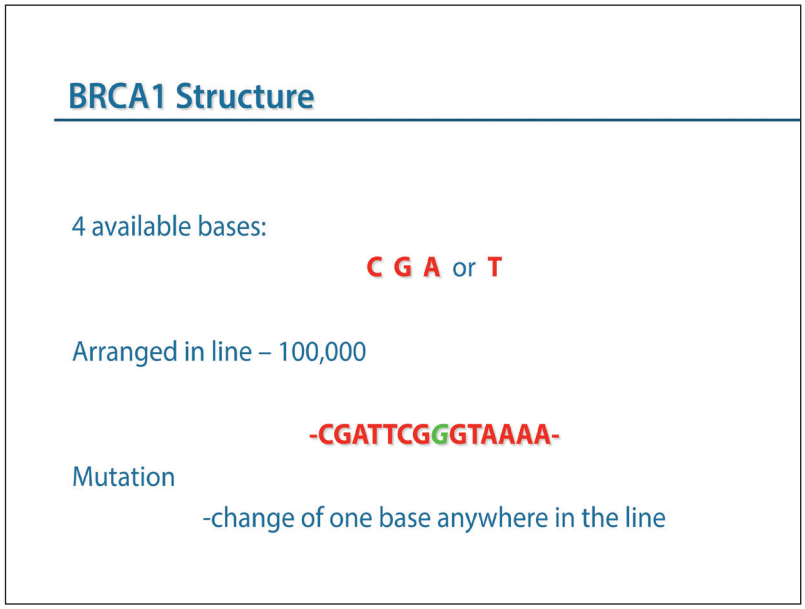
When a complete BRCA sequence is performed, there are three possible results produced by the laboratory;

1) the entire sequence of both genes has been examined and is normal.
2) both genes have been examined and a known, functionally important fault has been identified – a pathogenic mutation.
3) a variant in the sequence of BRCA1 or BRCA2 has been identified, but it is not known if it is functionally important or not – this will be reported by the laboratory as a Variant of Unknown Significance (VUS).

A VUS result can cause a great deal of uncertainty for the clinician, patient and family members. It is important for the clinician to get as much information as possible about that particular variant, as some of these variants will be true pathogenic mutations and therefore clinically important. Some laboratories will have tested in the region of a million samples and as a consequence have an extensive BRCA1/2 variant database and therefore a low VUS rate, published at <3%.

In families in which all affected relatives are dead, 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 then it is possible to offer testing as this is not covered by the NHS at present. If she is found to carry a pathogenic mutation then she is at high risk of developing breast and ovarian cancer. If she is found to carry

Figure 1: Diagrammatic representation of the BRCA genes showing a faulty copy.



two normal BRCA1/2 genes then 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.

Another recent change in clinical practice is to offer testing to patients who have developed triple negative breast cancer at a young age, without a significant family history. If a pathogenic BRCA1 or BRCA2 mutation is identified then that patient is at high risk of developing genetic ovarian cancer at some stage in her lifetime – clinically this is highly relevant information for that individual patient who may well consider having a prophylactic oophorectomy at some stage in the future. If she does not carry a pathogenic BRCA1/2 mutation her risk of developing ovarian cancer is similar to anyone else her age in the general population.

So, in summary the traditional service involves the following stages:

- careful history taking and pedigree drawing
- a brief description of the testing process
- highlighting the importance of VUS
- considering possible results and clinical implications
- result given by phone and early follow up appointment if needed

Inherited cancer gene panel testing

There are drawbacks to the traditional model of BRCA testing. In the majority of high risk families no mutation in BRCA1/2 is identified, and this drove the development of inherited cancer gene panel testing. This is a next generation model for assessing the risk of hereditary cancer. It allows for analysis of a larger number of genes targeting numerous cancer sites including breast, colorectal, ovarian, endometrial, gastric, pancreatic, melanoma and prostate. There are various panel tests available which look at varying numbers of genes in the panel. At the European Society of Human Genetics annual conference earlier this year, data looking at different gene panel tests (in this case using 27 and 42 gene panels) was presented. It showed that the detection of mutations within genes other than BRCA1 and BRCA2 highlights the genetic heterogeneity of Hereditary Breast and Ovarian Cancer (HBOC) [2,3]. A recently published study using a 25 gene panel demonstrated that there are 13 different genes that may be causative of hereditary breast cancer, 13 genes for hereditary colon cancer, and 9 genes for hereditary ovarian cancer [4]. Among these each gene has its own group of associated cancers, with its own spectrum of penetrance and expression, and with considerable overlap.

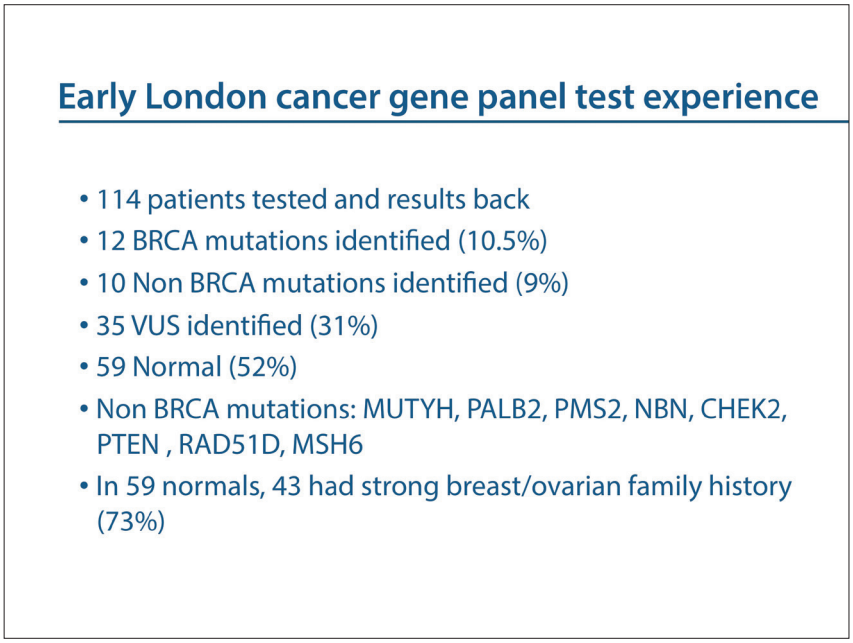
Various guidelines [5,6] support the use of panel testing based upon the ability to identify more mutations; improved time and cost-efficiency; and the provision of a solution to complex patient presentation and syndromic overlap. Nevertheless, there are still limitations to this model of testing, for example many practising clinicians may not understand the relevance of some of the genes in a panel, and it has been suggested that there are limited data regarding the degree of cancer risk associated with some of the genes on current panel tests. For some clinicians, if an unexpected genetic result comes through, it may be difficult to explain the implications to healthy family members. Therefore, it is important to select a panel test that specifically addresses such complexities by offering multiple clinical resources including the published risks associated with specific pathogenic mutations and the integration of societal management guidelines alongside the actual genetic test results. Furthermore, some organisations are partnering with academic institutions to run registration studies in order to advance research around less characterised genes associated with hereditary cancer [7]. Some guidelines in the US such as the National Comprehensive Cancer Network Guidelines (NCCN) have highlighted that multi-gene tests vary in technical specifications. However there are panel tests available which are analysed in a fully optimised laboratory and show 100% concordance with traditional methods such as Sanger Sequencing [8].

A specific panel test should not be selected unless all the genes are clinically actionable, i.e. according to guidelines there must be a screening recommendation made if a mutation is identified. Different laboratories have different times to produce the panel results and the patient should be given a realistic time line to expect results. Again we will phone the patient as soon as the result comes in and organise an early follow up appointment if needed.

Introducing a cancer gene panel testing service

Building on the traditional BRCA testing service outlined above, in panel testing, we start by taking a careful history and drawing a pedigree, then go on to talk about the gene panel testing process with reference to BRCA 1/2 testing, and the importance of selecting a test with a low VUS rate and what this would mean to the patient. We would then go

Figure 2: Our early experience of introducing an inherited cancer gene panel test into clinical practice in London.



on to discuss, in general terms, the panel of genes examined in order to explain that they cover several different cancer types. So in a family where we might expect to identify a BRCA1 mutation we might actually identify a mutation in one of the inherited bowel cancer genes.

Our early experience

We have tested 114 families and have identified pathogenic mutations in 12 families and pathogenic mutations in other genes in 10 families. By introducing a gene panel test rather than just offering BRCA testing, we have almost doubled the number of families in which we have identified clinically important cancer gene mutations. The most important clinical message however is that even when using a cancer gene panel test, in the majority of families tested, no pathogenic mutation has been identified, we should highlight the fact that there are many other important genes in inherited cancer which we are not yet able to test for.

Patients who have a normal gene panel test seem to be more reassured than patients who have a normal BRCA1/2 test. Inevitably there is professional discussion and disagreement about which specific genes should actually be in the panel chosen. However, in this article we have outlined the important clinical messages to convey to patients when introducing a new concept into clinical care; the idea of examining many different genes in one panel; and the same panel is examined in each family tested irrespective of the family history. We are convinced that offering multi-gene panel testing is a major step forward in clinical practice which has been generally welcomed by patients. We have built up clinical experience with a particular panel as part of a restricted early access programme which will be introduced into clinical practice globally over the next few months. It will be very interesting to establish whether our early experience in the London private sector is repeated across the UK and in other countries.

REFERENCES

1. Groep T, et al. *Pathology of hereditary breast cancer.* Cell Oncol. 2011; 34:71-88.
2. Castera L, et al. *Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes.* EJHG. 2014 Nov;22(11):1305-13.
3. Kurian A, et al. *Clinical Evaluation of a Multiple-Gene Sequencing Panel for Hereditary Cancer Risk Assessment.* J Clin Oncol. 14 April 2014. Advance online publication.
4. Tung N et al. *Frequency of mutations in individuals with breast cancer referred for BRCA1 and BRCA2 testing using next-generation sequencing with a 25-gene panel.* Cancer. 3 Sept 2014. Advance online publication.
5. The Society of Gynaecology Oncology: https://www.sgo.org/clinical-practice/guidelines/next-generation-cancer-gene-panels-versus-gene-by-gene-testing, March 2014.
6. National Comprehensive Cancer Network Guidelines Version 1.2014 Genetic/Familial High-Risk Assessment: Breast and Ovarian http://www.nccn.org/professionals/physician_gls/recently_updated.asp
7. Prospective Registry Of MultiPlex Testing https://connect.patientcrossroads.org/
8. Roa B, et al. *Development of a Next Generation Sequencing Panel to Assess Hereditary Cancer Risk that Includes Clinical Diagnostic Analysis of the BRCA1 and BRCA2 Genes.* Poster presented at the American Society of Human Genetics – October 24, 2013.