Mainstreaming Cancer Genetics (MCG)

Information Pack

Key Points

- Genetic information is important for people with cancer and their relatives.
- New gene testing methods can be harnessed so that more genes can be tested in more people, faster and more affordably.
- Processes for analysis and interpretation of genetic data are being developed so the right information gets to the right doctors at the right time to ensure people get the best management.
- The Royal Marsden NHS Foundation Trust has implemented a new 'mainstream' gene testing pathway which is much faster and less costly than the previous pathway.
- The mainstream pathway brings gene testing directly to the patient through their existing oncology appointments. Previously, patients could only have a gene test via referral to genetics departments.
- Over 300 cancer patients have had BRCA1 and BRCA2 gene testing through the new pathway. The response from patients and the cancer and genetic clinicians has been overwhelmingly positive.
- The gene testing is being performed in the new TGLclinical laboratory (www.tglclinical.com) which has state-of-the-art gene sequencing equipment which can do many more tests, much faster and at much lower cost than traditional testing methods.
- In 2013, NICE recommended people with >10% chance of having a mutation in either the BRCA1 and BRCA2 gene should be offered testing. This includes >10,000 cancer patients per year.
- The limited capacity and high costs of traditional gene testing pathways limits the BRCA1 and BRCA2 testing doctors are currently able to provide. The mainstream pathway could be used to deliver the NICE recommendations cost-effectively.

A Case Study: How patients can benefit from the 'mainstream' gene testing pathway

Patient C was diagnosed with breast cancer in 1999 at the age of 36. Following consultation with her doctors she decided to undergo a bilateral mastectomy and treatment with chemotherapy.

14 years later, Patient C was diagnosed with ovarian cancer and was treated with surgery and chemotherapy. Patient C was also offered gene testing by her oncologist through the mainstream pathway.

Patient C's gene test identified a mutation in the BRCA1 gene. The identification of this mutation, at this stage of her treatment, meant Patient C was eligible for treatment as part of a PARP inhibitor maintenance study.

Patient C is now undergoing treatment with a PARP inhibitor directly as a result of her gene testing through the mainstream pathway.

Patient C has also had an appointment with the Genetics team. Finding out that her cancers were due to a BRCA1 mutation now provides other members of the family with an opportunity to have a test to see if they also carry the mutation, should they wish to. For some this will show they have not inherited the mutation and are not at increased risk of cancer. For others it will show they have inherited the mutation. They will be at increased risk of cancer and can discuss and access surveillance and cancer risk-reducing interventions.

Patient survey of the mainstream gene testing pathway: results

A survey of ovarian cancer patients who have undergone gene testing via the mainstream gene testing pathway has been carried out by The Royal Marsden. The responses have been overwhelmingly positive. In particular, amongst the 105 patients that responded to the survey:

- 99% (104/105) of patients agreed or strongly agreed with the statement: 'I am pleased I had the genetic test.'

- 97% (102/105) of patients agreed or strongly agreed with the statement: 'I was happy to have the genetic test at one of my existing Oncology appointments rather than in a separate appointment with the Genetics team.'

Every woman with ovarian cancer offered a BRCA test chose to have testing. 17% of women with ovarian cancer tested were found to have a BRCA mutation.

Background Information about the MCG Programme

What is the Mainstreaming Cancer Genetics (MCG) programme?

Mainstreaming Cancer Genetics (MCG) is a clinical translational research programme, funded by the Wellcome Trust. It aims to develop the laboratory, analytical, interpretative and NHS clinical capabilities required to make cancer predisposition gene testing information routinely available in the clinic.

Why carry out this programme now?

Gene testing in people with cancer in the UK is currently limited, both with respect to the number of genes that can be tested and the number of people that can be tested. Recent technological advances provide the means to change that by making gene testing in large numbers fast and affordable.

What does the 'test' do?

There are three steps involved in the test. When we receive a person's blood sample the first step is generating the genetic data, which is often called 'sequencing'. The second is looking at the genetic data to identify mutations. This is often referred to as 'analysis'. The third is to understand what the data means for a person's health, which is often referred to as 'interpretation'.

The analogy of a book can be helpful. Sequencing is equivalent to generating all the letters in the book. Analysis is about making sure all the letters are in the right order with the correct punctuation and identifying all the typographical errors. Interpretation is about actually reading the book and understanding what, if any, difference the errors make to the meaning. This final stage is actually the most challenging and time-consuming part of the test.

Which genes will be tested?

The ICR, in partnership with Ilumina, Inc., has developed a new single test, called the TruSight™ Cancer panel which can analyse 97 cancer predisposition genes, in one go. These genes were included because they are proven to have clinically utility. The test will be upgraded to include more cancer predisposition genes as they are identified. Other parts of the genetic code relevant to cancer, for example influencing how an individual responds to cancer drugs, will also be included in due course.

A test in a single person generates, on average, 760 million letters of DNA code that require analysis (from 0.01% of the genome). On average, the analysis generates 117 mutations that require interpretation.

Will whole genome sequencing (WGS) make the programme obsolete?

No. On the contrary the programme will lay the foundations for whole genome sequencing to be used clinically in the NHS. We are currently using the TruSight™ Cancer panel which targets the <0.01% of the genome that is clinically useful to test in cancer patients. In the future we anticipate changing from TruSight™ Cancer to WGS, (as whole genome sequencing has some advantages), but all the other parts of the processes we are developing would still be used. Sequencing costs are falling and TruSight™ Cancer and WGS will, in time, be similar in cost. However, the time and cost of the full test will not change so rapidly as analysis and interpretation of WGS data is substantially more complex, time-consuming and costly.

How will the programme lead to more people having access to testing?

Access to gene testing is one of the major bottlenecks the programme is addressing. Traditionally, all cancer gene testing was undertaken by geneticists, doctors who are specialised in diagnosing genetic conditions. The programme is implementing a new model in which testing in cancer patients can also be done by oncologists, doctors who are specialised in treating cancer. Testing in people without cancer will continue to be done only by geneticists.

Many people with cancer are keen to have a gene test as soon as possible to help doctors plan the best treatment for them. The complex decision-making that people without cancer have to consider before having a test often doesn't apply. A more flexible system that makes the testing process simpler when appropriate will allow many more people to benefit from gene testing. Of course if people with cancer want more detailed discussions before deciding whether to have a test they can be referred to a geneticist in the standard fashion.

How will the programme benefit people with cancer?

Knowing if a person's cancer is due to a mutation in their genetic blueprint is very important. For example it can impact on which treatments may be more, or less, successful. It also gives information about future risks of cancer. People with cancer predisposition gene mutations are often at risk of getting another cancer and may choose to have more comprehensive surgery, or may need extra monitoring.

Will the programme have benefit for people without cancer?

Yes, the programme will be very helpful for families of people with cancer, who are often concerned about their own cancer risks. Knowing if their relative's cancer was due to a gene mutation provides important information. If no mutation is found, it will be reassuring in suggesting that there is unlikely to be a high-risk of cancer for family members. If a mutation is found then relatives can have a specific test to see if they also have the mutation. Those that do have the mutation can have screening and prevention strategies, where appropriate. Those that do not have the mutation can be reassured.

Will anyone with cancer be able to benefit from the programme?

We hope so. The programme aims to make the entire process of gene testing in cancer patients as practical, robust, efficient and cost-effective as possible.

The mainstream model of gene testing has been successfully implemented at the Royal Marsden. The resources developed for use at the Royal Marsden have now been made freely available for other hospitals wishing to implement a similar service (www.mcgprogramme.com/brcatesting).

We will also be producing data about the health and cost effectiveness of gene testing in cancer patients so that the NHS can make an evidence-based decision about it.

Cancer Genetics – some basic facts

What is the genome?

The term ‘genome‘ is used to describe our entire genetic information present in each of our cells. The genome is made of DNA which is itself made of 4 building blocks denoted by the letters A, C, G, T. The order and position of the letters determines the function of that part of the genome. The human genome contains over 3 billion letters.

What is a gene?

Genes are the parts of the genome that code for proteins, which in turn provide the instructions that make our bodies work. There are about 20,000 genes in the genome. The genes only take up 1% of the genome.

What does sequencing mean?

The order of letters in the DNA code is the ‘sequence’. The term sequencing has come to mean the reading of the DNA code, either of selected parts or the whole genome. There has been a major advance in sequencing over the last five years. Previously the code had to be read one letter at a time. The newer methods, which are sometimes called next-generation sequencing or NGS, can read millions of sections of the genome simultaneously. This has made the process of sequencing much, much faster and cheaper.

What is a mutation?

A mutation is a change in the DNA code. There are many different types of mutation. For example single letter changes, removal or insertion of letters or rearrangement of letters. We all have many thousands of mutations but they are almost all innocuous.

How are gene mutations involved in cancer?

There are two ways in which gene mutations can be important in cancer.

1) Mutations in the DNA of the cancer cells can help cancers to grow and spread. These mutations are not present in normal cells; they are restricted to the cancer. They are sometimes called ‘somatic’ mutations.
2) Mutations that are present in every cell in the body and make it more likely that a normal cell will turn into a cancer cell. Such mutations are either inherited or can start for the first time at conception. Sometimes they can be passed on to offspring. Such mutations are called ‘germline’ or ‘constitutional’ mutations.

What is a cancer predisposition gene?

Genes in which germline mutations can increase the risk of cancer are called ‘cancer predisposition genes’. These mutations do not cause cancer (otherwise every cell in the body would be a cancer), but they do predispose to cancer as they make it much more likely that at least one of the cells in the body will turn into a cancer cell. There are currently close to 100 known cancer predisposition genes, together predisposing to about 35 different cancers. We estimate that at least 1 in 100 people have a cancer predisposition gene mutation. The frequency is much higher in cancer patients, for example about 1 in 7 women with ovarian cancer have a cancer predisposition gene mutation and about 1 in 3 people with certain endocrine cancers.

How many cancers are genetic?

It depends what one means by ‘genetic’. Somatic mutations are a hallmark of cancer. The great majority of cancers will have some mutations in the cancer cells, and therefore could be considered ‘genetic’. However, most people use ‘genetic’ to mean ‘hereditary’. Somatic mutations are not hereditary. Germline mutations in cancer predisposition genes are often hereditary. Overall about 2% of cancers (~7000 people each year) develop because of a cancer predisposition gene mutation. This is not evenly distributed between cancers. For example ~40% of some childhood cancers, ~15% of ovarian cancers but only a very small number of lung cancers are due to currently known cancer predisposition gene mutations.

Key Partners in the MCG programme

ICR The Institute of Cancer Research

The Institute of Cancer Research, London, is one of the world's most influential cancer research institutes, with an outstanding record of achievement dating back more than 100 years. Professor Nazneen Rahman, principal investigator for the MCG Programme, is Head of the Division of Genetics and Epidemiology at the ICR.
For more information visit www.icr.ac.uk

wellcome trust

The Wellcome Trust is a global charitable foundation dedicated to achieving extraordinary improvements in human and animal health. It supports the brightest minds in biomedical research and the medical humanities. The Wellcome Trust funds the MCG Programme, as one of its strategic awards.
For more information visit www.wellcome.ac.uk

The ROYAL MARSDEN NHS Foundation Trust

The Royal Marsden is a world-leading cancer centre specialising in cancer diagnosis, treatment, research and education. As a key part of the MCG programme, multiple clinical units at the Royal Marsden will pilot the integration of gene testing in cancer treatment. Professor Nazneen Rahman, principal investigator for the MCG Programme, is Head of the Cancer Genetics Clinical Unit at The Royal Marsden.
For more information, visit www.royalmarsden.nhs.uk

The Wellcome Trust Centre for Human Genetics

UNIVERSITY OF OXFORD

The Wellcome Trust Centre for Human Genetics (WTCHG) is a research institute of the University of Oxford, funded by the University, the Wellcome Trust and numerous other sponsors. Their objective is to undertake research into the genetic basis of common conditions. Researchers from the WTCHG are working with the programme to develop the analytical methods required to analyse genetic information of relevance to cancer.
For more information, visit: www.well.ox.ac.uk

illumina®

Illumina, Inc. is a market leader in developing integrated systems for the analysis of genetic variation and biological function. Illumina, Inc. has worked in partnership with the ICR to develop the Cancer predisposition gene test which is now commercially available, marketed as the TruSight™ Cancer panel.
For more information, visit: www.illumina.com