

# Breast Cancer Campaign submission to the House of Lords Science and Technology Committee inquiry on Genomic Medicine

*April 2008*

## **Summary of key points**

- There has been a substantial amount of genomic information gathered that has helped us to better understand why and how diseases such as breast cancer develop
- New technologies have become more readily available to researchers enabling progress to be made
- There is great potential for genomic research to build on the progress made so far, resulting in substantial translational benefits to patients in the future
- New developments in identifying genes of low penetrance\* offer promising signs that in the future a greater number of those at high risk of disease will be identified
- There is a need for much more cross-disciplinary working within genomic research
- Future research should be focussed upon addressing the gaps in current knowledge and funding should be prioritised accordingly
- Advances in research rely on having appropriate technologies and tissues available and on training for scientists and clinicians
- The application of computational tools such as bioinformatics has become essential to utilise the vast amounts of genomic data
- Further genomic research will enable better combinations of treatment to be used
- The reliability of genetic testing could be substantially improved through further genomic research, leading to direct benefits to patients through improved medical advice
- Biomarkers can identify those patients that are likely or unlikely to respond to a particular therapy, leading to a better use of resources that is more sensitive to patients
- There is an urgent need for genetic material to become more readily available, as a shortage of resources will hinder future progress through research
- Improved genomic information will allow clinicians to give a more accurate diagnosis for patients, and to recommend more specialised treatments as a result

\* Please see glossary of terms provided

## 1. Introduction

1.1 Breast Cancer Campaign welcomes the opportunity to submit evidence to the House of Lords Science and Technology Committee inquiry on Genomic Medicine. The inquiry aims to provide an assessment of genomic technologies and their actual and potential impact on clinical practice. This paper refers to the specific aspects of the inquiry's terms of reference that are of direct relevance to the research that Breast Cancer Campaign funds.

1.2 We specialise in funding innovative world-class research to understand how breast cancer develops, leading to improved diagnosis, treatment, prevention and cure. We aim to be the leading specialist in breast cancer research across the UK and the Republic of Ireland, making a significant impact on breast cancer for the benefit of patients. We currently fund 107 projects throughout the UK worth over £13.1 million.

1.3 Breast Cancer Campaign believes that genomic medicine is a vital research priority for breast cancer research, one that requires wholehearted government support. Almost a third of the charity's 107 research projects are focused within this area. To illustrate its potential value to patients we have used examples of our research below. We believe that further analysis of the genome will provide a better understanding of numerous diseases, including breast cancer, leading to improved, targeted treatments tailored to individual patients.

1.4 This document has been prepared in consultation with a selection of Campaign's current researchers whose research interests lie in genomic medicine.

## 2. Research and Scientific Development

- What is the state of the science? What new developments are there?
- How much collaboration is there?
- What are the current research priorities

### State of the science

2.1 Breast Cancer Campaign has recently led a ground-breaking project to identify where further research needs to be done that would bring the greatest benefit to patients. The breast cancer research gap analysis<sup>1</sup> has recently been published, bringing together the expertise of 56 eminent breast cancer researchers to identify the limitations of current research into the pathophysiology, detection, treatment, prevention and psychosocial aspects of breast cancer.

2.2 From the genomic knowledge that research has already cultivated, we understand that there are multiple genes of varying degrees of penetrance that are involved in predisposition to breast cancer. Genome wide screens and somatic genetic approaches are continuing to identify further genes involved in breast cancer.

2.3 Both BRCA1 and BRCA2 are well known to be breast cancer susceptibility genes of high penetrance, accounting for up to 10 per cent of all cases of breast cancer. However, the overall knowledge on their actions within the body is far from complete. Similarly, there are limitations in the current knowledge of the large scale genetic rearrangements that occur in

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<sup>1</sup> Thompson et al., Evaluation of the current knowledge limitations in breast cancer research: a gap analysis. *Breast Cancer Research* 2008, 10:R26.  
<http://breast-cancer-research.com/content/10/2/R26>

tumour cells, which is required to give us a better understanding of how breast cancer develops. Low penetrance genes are also a key area for research to focus upon, and there is a need for better knowledge on how their variations affect and interact upon the risk of breast cancer. Research around the world over the last five to 10 years has been largely unsuccessful in identifying common breast cancer gene variants until now. This type of low penetrance variant requires very large studies that can only be successfully achieved through collaboration, both between research centres and between scientists and doctors.

## **New developments**

2.4 In 2007, Professor Doug Easton and colleagues, published a study in *Nature* outlining the discovery of five new low penetrance genes thought to be involved in breast cancer development. The study compared the genes of 20,000 breast cancer samples and 20,000 normal samples and discovered genetic mutations in five genes that have between a 10-35 per cent risk of developing breast cancer.

2.5 In a new study funded by Breast Cancer Campaign, Professor Easton is now focusing on one of those five genes, TNRC9, which is found in high levels in breast cancer cells that metastasise quickly. This project aims to find out exactly what part of the gene the mutation occurs in, and will study the gene in breast cancer and normal cells in the laboratory to ascertain its role in aiding breast cancer cell growth and metastasis. The effects of the gene in breast cancer metastasis will also be examined in mouse models. The combined results should provide exciting new information on the gene's involvement with breast cancer, which could lead to genetic testing for the gene or to treatments tailored to those with the variant.

## **Collaboration**

2.6 One of the main generic needs relevant to all areas of our breast cancer research gap analysis was the necessity of much more cross-disciplinary working, and this is certainly the case within genomic research. There is a serious need for networks of collaboration to be fully established that include the provision to collaborate on areas of genomic research. The current initiatives fostering collaboration within the UK tend to focus on specific funders of research, for example the Medical Research Council and the NHS. There is presently no initiative to involve all funders of research in collaboration, and we believe that this will continue to slow down advancement across all areas of research.

2.7 Collaboration is paramount to ensuring that our genomic knowledge in areas such as biomarkers is increased as quickly as possible, but also to ensuring that the knowledge gained is used to its fullest extent in all areas of research that may benefit from it. Developing new collaborative initiatives, which would be multidisciplinary and involve public, charity and pharmaceutical funded research, would provide an important opportunity for this knowledge to be more widely expanded.

## **Research priorities – addressing the gaps**

2.8 For knowledge on gene variants to be significantly improved through research, a number of obstacles need to be overcome. Such research relies upon large supplies of high quality genetic material that is easily accessible to those that require it. At present this is not readily available to all researchers. Large scale experiments, such as gene sequencing, are also extremely expensive to conduct, and so large levels of funding are required for this type of research to be carried out successfully. This will also result in an enormous amount of information, which cannot be easily analysed without expert bioinformatic analysts.

2.9 The benefits to patients through further genomic research will have significant implications for breast cancer patients in three key areas:

- Comprehensive genomic knowledge will lead to a substantially improved estimation of genetic risk of breast cancer
- Classifying individual breast tumours according to genetic information will help to predict a more accurate prognosis in addition to more accurately predicting the efficacy of treatment
- Research will lead to the creation of new therapies targeted to patients of a particular genomic makeup

### **3. Data use and Interpretation**

- Is genomic information published, annotated and presented in a useful way? Should there be a common, public database? If so, who should fund, and have responsibility for, such an initiative?

3.1 With the quantity of genomic data that has emerged from cancer research in recent years vastly increasing, the application of computational tools such as bioinformatics has become essential. In 2003, the National Cancer Research Institute (NCRI) established the NCRI Informatics Initiative, aiming to bring together data gained in every area of cancer science and medicine into one fully integrated and accessible knowledge base.

3.2 The data currently produced from research ranges from genomic information to large population studies, and it is hoped that by having a central access point for this data new avenues for research will be opened up. Making this data available and accessible will streamline the translation of cancer research into better prevention, treatment and care. The Initiative has formed international links with similar programmes in the United States and Europe, such as the US National Cancer Institute Centre for Bioinformatics, which further adds to the pool of information available to researchers.

3.3 From 2008, Breast Cancer Campaign will include in the terms and conditions of all our research grants a recommendation that the research teams deposit all of their findings with the NCRI Informatics Initiative. We believe that this is a vital means of ensuring that the findings of our research are used to their fullest potential.

### **4. Translation**

- What opportunities are there for diagnostics, therapeutics and prognostics - now and in the future?
- How meaningful are genetic tests which use genome variation data?

#### **Future opportunities for diagnostics, therapeutics and prognostics**

4.1 Our breast cancer research gap analysis highlights that there is an incomplete understanding of the biology of breast cancer. For example, we are still unable to determine why certain cancers metastasise and others resist certain drugs. The gap analysis indicates that there is a need to increase this knowledge in order to create therapies tailored to the individual. An enhanced understanding of the sequencing, combinations and durations of treatments could have significant translational benefits in the future. It could also result in

financial benefits by ensuring that treatments are not provided to those that genomic testing has indicated would not respond.

4.2 Dr Jennifer Quinn and Professor Paul Harkin are both carrying out work funded by Breast Cancer Campaign at Queen's University in Belfast, investigating the genomic relationship on the efficacy of certain breast cancer treatments. The BRCA1 gene regulates cell growth in the breast, and the loss of the gene is a significant factor in the development of both inherited and sporadic breast cancer. Chemotherapy drugs work by damaging the DNA in cells or by preventing cell division. Dr Quinn's work showed that the loss of the BRCA1 gene may make tumours more responsive to chemotherapy that acts by damaging DNA, with the presence of BRCA1 making tumour cells resistant to the same treatment.

4.3 Working together with Professor Harkin, Dr Quinn aims to understand the mechanism by which BRCA1 has this important effect on DNA damage based chemotherapy. She believes that BRCA1 switches on or off key target genes that then make the tumour resistant or sensitive to the chemotherapy. Rather than access these genes one by one, DNA Chip technology allows her to screen thousands of genes simultaneously. ChIP on chip analysis and high throughput siRNA based screening will then find which BRCA1 target genes are most important in mediating this effect. This will ultimately result in the identification of BRCA1 target genes that will represent markers of response or resistance to DNA damage based chemotherapy. We believe that this will then lead to a targeting of breast cancer drug development strategies.

4.4 For the prospects of advancement in this area, resources should be put in place to provide for the collection of high quality clinical material from breast cancer patients before and during treatment, which would include primary tumours as well as metastatic deposits. Genomic research is dependent on the availability of appropriate technologies and tissues and on training for scientists and clinicians. The type of research mentioned above simply could not take place without state of the art techniques such as DNA Chip technology.

4.5 There is also a need for an effective monitoring system to record the response to and development of resistance to therapy, as well as early disease progression, in order to ensure that this information is readily accessible and simple to collect.

4.6 Research should also examine the role of the tumour microenvironment and the immune system in the development and treatment of breast cancer.

### **Efficacy of current genetic testing**

4.7 Current genetic testing allows people to have their DNA tested to find out whether the breast cancer susceptibility genes, BRCA1 and BRCA2, are unaltered and so operating normally. Those with a family history of the disease often have mutations in these high penetrance genes, which have up to an 85 per cent lifetime risk of developing breast and ovarian cancer. Currently, however, testing cannot distinguish between the many different mutations that may have happened to BRCA1 and BRCA2, only that they are mutated.

4.8 It is possible that in some cases where a BRCA1 and BRCA2 mutation will have been identified, the resultant effect will prove to be relatively insignificant. Mutations to these two genes generally tend to result in the production of shorter proteins, and it is this that may then lead to cancer forming. However, some mutations to BRCA1 and BRCA2 are more subtle than this, and their effects are less easy to predict. Not all alterations to these genes will lead to breast cancer developing.

4.9 Dr Joanna Morris is being funded by Breast Cancer Campaign to examine this further at King's College, London. The focus of her work is centred on a particular region of the BRCA1 gene where these subtle mutations occur, in order to ascertain whether these lead to the development of breast cancer. With a clearer picture of which precise mutations to the BRCA1 gene lead to breast cancer, genetic testing will be made more accurate. This will have direct benefits in ensuring that those people that have a relatively harmless mutated gene will not have any unnecessary preventative interventions such as prophylactic mastectomies.

## 5. Disease Markers in Breast Cancer

- In what way do genome-wide association studies contribute to the identification of biomarkers? How is the study of genetic factors and biomarkers integrated for translational purposes?

5.1 Presently, patient groups can be successfully stratified in clinical trial by using biomarkers, an example being according to HER2 positive receptors expressed by breast cancer cells. Identifying these types of biomarkers can have direct translational benefit through accurately recognising which of the five specific types of breast cancer a patient has, in addition to accurately predicting which patients are most and least likely to respond to a particular treatment.

5.2 Our breast cancer research gap analysis has highlighted several key areas that require immediate focus for research. Disease marker concepts should be applied to trials of treatments for pre-invasive disease including ductal carcinoma in situ and to models of sentinel lymph node assessment, where funding is limited and where long-term follow-up is required to obtain robust clinical data, but where we need a better understanding of the pathophysiological processes involved.

5.3 Clinical, radiological, pathological and genomic data is not currently combined in trial populations, and no robust validated markers have yet been developed for predicting a patient's response to chemotherapy or radiotherapy. There is also a serious need for improved prognostic indices based on disease markers, and no consensus exists for markers indicative of resistance to therapy.

5.4 Such markers have been proposed (for example ER-positive, PgR-negative tamoxifen-resistant cancers), but there is little agreement about methodology or cut-offs of scores for clinical application, or indeed their overall value. In addition, some markers may not be useful once regimens or therapies are superseded. We therefore need to compare, and potentially combine, markers such as the ER and PgR with pathological markers (such as histological type, grade and node metastasis), which have prognostic importance. Funding for robust studies evaluating these markers is crucial, but is rarely achieved without financial support from the pharmaceutical industry.

5.5 Barriers have also been identified that are hindering this promising area from further development. Any new assays that are developed must stand up to the day-to-day challenges of clinical practice, of which the current quality is highly variable. RNA-dependent assays have for example been considered less robust than protein- or DNA-based assays in the breast cancer setting.

5.6 There is also a strong need for tissue handling to be standardised. Clinical trials have rarely developed standard procedures for collecting and documenting tissue, although

more recent, innovative trials do so. Even then, delivery time and costs may prevent techniques and markers from being widely used in clinical practice. In addition, the impact of some legislation (such as *Good Clinical Practice* and *Good Laboratory Practice*) and ethical approval processes on the funding, management, ownership and access to tissue collections and associated clinical data have both affected the development, choice and use of markers. Academic pressures (particularly the influence in the UK of the Research Assessment Exercise) may also be counterproductive to collaborative translational research, which should (but may not be) recognised as of high value.

5.7 We believe therefore that for the progress in the area of biomarkers to move forward, there is a need to:

- Design innovative trials and translational studies to develop and evaluate predictive and prognostic markers
- Develop close multidisciplinary collaboration with high-quality histopathology and rigorous scientific assessments to validate new markers important for patient outcome
- Identify robust markers of resistance or sensitivity to therapy that can be applied across the spectrum of breast disease from screen-detected to metastatic breast cancer

## 6. Use of genomic information in a healthcare setting

- What impact will genomic information have on the classification of disease?
- How useful will genomic information be as part of individualised medical advice?

### Disease classification

6.1 As genomic knowledge increases, clinicians will be able to make better diagnoses and treat breast cancer more effectively. The genetic information obtained from breast cancer cells can be studied to discover important information that will help clinicians to select the most appropriate treatment.

6.2 Genetic information that impacts on disease classification has been discovered by Dr Andrew Green, who holds a grant funded by Breast Cancer Campaign at the University of Nottingham. Dr Green has identified six new distinct types of breast cancer that reveals information on patients' long-term survival and response to treatment. These six different variations of breast cancer are distinguishable by the different proteins present within the cancer tissue, with each class associated with different rates.

6.3 Dr Green hopes this discovery will allow clinicians to give a more accurate diagnosis for breast cancer patients by classifying their cancer to the types identified, and to recommend more specialised treatments that will be more effective. By identifying at the point of diagnosis how precisely a person's breast cancer will develop, clinicians will be able to decide on the best treatments specific to that patient, providing them with the best possible chance of recovery.

6.4 On diagnosis of breast cancer, a patient may be offered a variety of different treatments by their clinician. In the majority of cases of breast cancer, patients will receive radiotherapy as a means of destroying any breast cancer cells that remain post-surgery. This has proven to be a very effective treatment, but for a small number of patients it can result in adverse side-effects. At the end of treatment, some experience marked redness and peeling of the skin, which usually rapidly heals. Others will at a later stage develop unsightly red blood vessels or thickening beneath the skin, often associated with chronic pain, which are lifelong.

6.5 It is currently impossible to identify which patients are susceptible to these side-effects prior to receiving treatment. In a project funded by Breast Cancer Campaign, Dr Paul Symonds of the University of Leicester is attempting to determine whether there is a genomic explanation as to why these side-effects occur for some patients after receiving radiotherapy. By examining the genes of 1000 patients, Dr Symonds is aiming to identify those genes that are crucial in determining whether a patient will exhibit these adverse reactions. Ultimately this study could lead to a test to identify those that are most likely to be subject to these side-effects, enabling clinicians to advise patients of these risks prior to treatment.

## **7. In Summary**

7.1 Breast Cancer Campaign believes that genomic medicine has enormous potential to ensure significant clinical benefits to patients in the future. The progress already made has enabled the research community to better understand the causes and mechanics of diseases such as breast cancer, and further investment is needed to take this forward.

7.2 The projects referenced in this submission provide just some of the exciting genomic research that Breast Cancer Campaign currently funds. We believe that research is the start of the solution, and that for the full benefits of genomic medicine to be realised in the future it is essential that both the gaps and barriers in research are addressed. We believe that genomic medicine will become a key part of future treatments, and we are confident that by utilising state-of-the-art technologies we will soon see more translational benefits for patients.

## **Glossary of terms**

Bioinformatics – the application of computational techniques to the management and analysis of biological information

Chemotherapy – use of chemical agents in the treatment or control of disease

ChIP on chip – a technique for isolation and identification of the DNA sequences occupied by specific DNA binding proteins in cells. Also known as genome-wide location analysis

DNA – deoxyribonucleic acid, one of two types of molecules that encode genetic information

Ductal carcinoma in situ – a condition whereby the cells lining the milk ducts (the channels in the breast that carry milk to the nipple) are cancerous, but stay contained within the ducts without growing through into the surrounding breast tissue

ER-positive – term used to describe a breast tumour that contains estrogen receptors and is therefore likely to respond to treatment with Tamoxifen

Gene sequencing – determination of the sequence of nucleotide bases in a strand of DNA

Herceptin – drug used to treat breast cancer that is HER2-positive and has spread after treatment with other drugs

Histopathology – the study of the microscopic anatomical changes in diseased tissue

Metastasis – the process by which cancer spreads from the place at which it first arose as a primary tumour to distant locations

Pathophysiology – the functional changes associated with or resulting from disease

Penetrance – the degree of regularity with which a gene produces its specific effect in its carriers in a population

PgR-negative - term used to describe a breast tumour that lacks progesterone receptors, prophylactic mastectomies – surgery to reduce the risk of developing breast cancer by removing one or both breasts before disease develops

Radiotherapy – the treatment of disease with ionizing radiation

RNA – ribonucleic acid, a nucleic acid molecule similar to DNA but containing ribose rather than deoxyribose

Sentinel lymph node – the first lymph node to which cancer is likely to spread from the primary tumour

siRNA based screening – a method used to identify gene targets for the development of new treatments

Tamoxifen - a nonsteroidal oestrogen antagonist used in the treatment of advanced breast cancer in women whose tumours are oestrogen-dependent and also used prophylactically by some women at risk for breast cancer