Project Information Sheet - Epigenetic Silencing of BRCA2 & PALB2

"There are so many people slipping through the net. If you test positive for the BRCA gene mutation you are monitored from an early age. I tested negative, so they didn't deem me high risk, but it still could be genetic and that's why the research Prevent Breast Cancer is doing is so important."

Paula Eardley, breast cancer survivor and Prevent Breast Cancer supporter

About Prevent Breast Cancer

Predict. Prevent. Protect. You could call it our mantra. As the only UK charity entirely dedicated to the prediction and prevention of breast cancer, we're committed to freeing the world from the disease altogether. Unlike many cancer charities, we're focused on preventing, rather than curing. Promoting early diagnosis, screening and lifestyle changes, we believe we can stop the problem before it starts. As we are situated at the only breast cancer prevention centre in the UK, we're right at the front line in the fight against the disease.

We predict – by identifying who is at risk of breast cancer
We prevent – by offering preventative interventions, to **stop** breast cancer before it starts
We protect – our goal is to **shield future generations** from breast cancer

Prevent Breast Cancer seeks to create a breast cancer free future for the next generation. We conduct ground-breaking research into the prediction and prevention of breast cancer. Our research falls under four different categories: gene research, early detection and screening, preventative drugs, and diet and lifestyle.

We are a registered with the Charity Commission in England with the Registered Charity Number 1109839.

About this project

Funding Request

Our new **gene research** project focuses on a biological mechanism whereby gene malfunctions that greatly increase a woman's risk of getting breast cancer may be left **undetectable by standard gene testing**. This is a two-year project running from July 2019 – July 2021.

The Need

Breast cancer is the most common cancer in the UK, accounting for a staggering 15% of all cancer diagnoses. Across the UK, 150 individuals are diagnosed with breast cancer every day. Tragically 32 of them will lose their fight against the disease. Unfortunately, these figures are rising. If trends continue, we can expect a 2% increase in diagnoses by 2035.

Unfortunately, many women with inherited breast cancer do not have an exact explanation for their diagnosis. For many years we have understood that women with **genetic mutations in their BRCA1, BRCA2 or PALB2 genes** are more likely to:

- develop breast cancer at a young age
- develop a more aggressive form of breast cancer
- have cancer in both breasts
- develop additional cancers such as ovarian and pancreatic
- find that many people in their family develop breast cancer, including men

However often when many of these women opt for gene testing, the test comes back negative. In fact, the high-profile genetic changes such as BRCA1, BRCA2 and PALB2 are **only present in 5-10% of people who are diagnosed**. This means that there may be other important genetic markers that current tests are not picking up.

Our researchers have recently found a new biological mechanism called "epigenetic silencing" that stops the gene BRCA1 from working in some individuals, causing the familial breast cancer symptoms listed on the previous page. **What if this is also the case for BRCA2 and PALB2**?

It is vitally important this question is answered, because if there is a fault with these genes that current tests are not picking up, these women are sadly missing out on effective measures to reduce their risk of getting breast cancer such as additional screenings or preventative surgery. It could also mean that they will **not be offered the most effective treatment** if they do develop breast cancer.

The Methods

To determine whether epigenetic silencing is taking place, our teams will look at the genes of individuals from high-risk families with breast and ovarian cancer, prioritizing those who have pancreatic cancer and male breast cancer (over 400 samples have already been already been obtained and more are available). The team will run tests such as RNA analysis and targeted whole genome sequencing to find out whether these genes are not functioning correctly due to epigenetic silencing.

When we ran these tests on 49 families with symptoms of genetic breast cancer, we found that epigenetic silencing of the BRCA1 gene was taking place in 2 of these families. On a larger scale and with the inclusion of BRCA2 and PALB2, this number could represent a huge percentage of those with a high risk of breast cancer.

Impact

This work has the potential to change the lives of many individuals who find they are experiencing **the same patterns of cancer diagnoses in their families but have found that gene testing comes back negative**. We predict that this will significantly increase the number of people who will benefit from gene testing. Affected families will then get access to support such as early and more frequent cancer screenings and more suitable treatments, such as the use of PARP inhibitors.

Project Leader

The PI of this research project is Professor William Newman, Professor of Translational Genomic Medicine at Manchester University, expert in the field with over 211 publications and specialist in breast cancer research.

The co-applicant is Professor D Gareth Evans, Professor of Medical Genetics and Cancer Epidemiology, The University of Manchester and Consultant in Medical Genetics and Cancer Epidemiology, Central Manchester Hospitals NHS Foundation Trust and The Christie NHS Foundation Trust. He has published 709 peer reviewed publications (264 as lead author). Professor Evans has set up a nationally regarded clinical service for cancer genetics in the North West region and is clinical lead of the NICE Familial Breast Cancer Guideline Group.

More Information

For more information about this project, please get in touch with Vicki Wilkinson, our **Trusts, Relationships and Research Manager** by emailing vicki@preventbreastcancer.org.uk or phoning 0161 291 4402