The University of Manchester

MANCHESTER CANCER RESEARCH CENTRE

Manchester Breast Centre
From Molecular Science to the Clinic

MANCHESTER BREAST CENTRE

REPORT 2019-2020

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EXECUTIVE **SUMMARY**

Welcome

Rob Clarke, Director of Manchester Breast Centre

It is a pleasure to introduce this report of the Manchester Breast Centre (MBC). The MBC was founded by Tony Howell, Charles Streuli and Nigel Bundred in 2005, with the aim of bringing together Manchester's basic and clinical breast researchers.

We started with 7 Principal Investigators whose research was focused on the breast and breast cancer, but we quickly grew and gained recognition as a centre for breast research within the Manchester Cancer Research Centre, a partnership between The University of Manchester, Cancer Research UK and The Christie NHS Foundation Trust. Over the years, we have matured into a collaborative group numbering 21 Principal Investigators and 16 Associate Members (breastcentre.manchester.ac.uk).
We have a large body of research support including more than 60 post-doctoral research associates, research assistants, research nurses and dieticians. We train large numbers of clinical fellows and non-clinical scientists carrying out PhD research projects. Currently, MBC comprises over 100 researchers funded by a broad spectrum of governmental and charity sources (**page 43**). Our grouping of 37 Research Academics has become a hub for basic and translational breast research, and we are now one of the largest collective group of basic and clinical breast researchers worldwide.

We continue to attract new researchers and over the past 2 years have welcomed Principal Investigators Sankari Nagarajan from the CRUK Cambridge Institute, Rajiv Dave, a breast surgeon with the Manchester University NHS Foundation Trust, and Ciara O'Brien, a Medical Oncologist who did her PhD studies with us. Also, we welcomed Kaye Williams, Nisha Ali, Kate Williams, Santiago Zelanay and Jamie Honeychurch, all from Manchester who have joined as Associate Members.

The aim of the MBC is to translate our research findings from the laboratory into the clinic, thereby improving the prevention and treatment of breast cancer. Achieving this objective requires highly collaborative research and 'team science'. This ethos is evidenced by the many peer-reviewed publications whose authorship is shared by several Principal Investigators and Associate Members. In this Report, we highlight our research and publications over the past two years. In 2019 and 2020, MBC researchers published 140 papers, of which more than 25% were published in highly respected journals with an impact factor of greater than 10.

The MBC is focused on four broad areas of investigation comprising basic laboratory research, risk and prevention studies, surgical studies including surgically-related trials, and oncology trials (**page 10**). There is a large overlap between basic and clinical research, which results in reciprocal interactions between the two, resulting in novel translational strategies.

The impact of MBC research on the clinic is well demonstrated by work on risk estimation, screening and prevention, and the numerous investigator-led surgical and oncology trials to improve the outcome of women diagnosed with breast cancer (**pages 5-9**).

The research carried out in 2019-20 is described in the reports on **pages 11-37**. There are many highlights including new laboratory findings on the prevention of bone metastasis and combatting endocrine resistance;

an update of the IBISII anastrozole prevention trial; the use of Artificial Intelligence to automate the determination of mammographic density; breast reconstruction; assessing Ki67 response to endocrine therapy at surgery; the importance of PARP and Akt inhibitors to treat advanced breast cancer; and using circulating tumour DNA to guide treatment in Phase 1 clinical trials (Papers highlighted in research reports).

MBC researchers have celebrated success in 2019-20 through recognition by their peers. Professor Gareth Evans published his 1000th research paper and was elected a Fellow of the Learned Society of Wales and Fellow of the Royal College of Obstetrics and Gynaecology. Professor Tony Howell received a prestigious lifetime achievement cancer prevention award from the International Cancer Prevention Institute in Switzerland. Several Principal Investigators were promoted to Professor (Sue Astley as a Professor of Intelligent Medical Imaging, Cliona Kirwan as a Professor of Surgical Trials, and Rob Clarke as a Professor of Breast Biology). Our young scientists also celebrated success: Dr Rachel Eyre was awarded the Sir Anthony Driver prize for the Breast Cancer Now Researcher of the Year 2019 (see photo below); Dr Angélica Santiago-Gómez won the best selected oral presentation prize at the British Association for Cancer Research Special Conference on Breast Cancer in Newcastle in October 2019; and Elke van Veen was the University of Manchester Doctoral College Postgraduate research student of the year in 2019.

Baroness Delyth Morgan, Chief Executive of Breast Cancer Now (right), presenting Dr Rachel Eyre with the Driver prize.

MBC has welcomed and hosted high profile basic and clinical researchers from the UK, Europe and around the world to present Breast Cancer Now-sponsored seminars, and to meet and discuss research (**page 39**). Our own researchers are much in demand at the national and international level to give seminars and lectures at prestigious conferences such as the AACR Annual San Antonio Breast Cancer Symposium (Rob Clarke), the Gordon Research Conference on Mammary Gland Biology (Charles Streuli), the European Breast Cancer Conference (Gareth Evans) and the American Society for Clinical Oncology Annual Conference (Sacha Howell).

MBC has long been an advocate of patient and public engagement to inform on research, and to receive valued input. We invite patient advocates to take part in our events, and run public engagement events such as Open Days. Recently we held a virtual outreach event to celebrate Breast Cancer Awareness Month, and to mark 'Wear It Pink' day, by hosting a series of talks and discussion on "How can we predict and prevent breast cancer now?" (report on **page 38**).

We hope that you are interested by this 2019-20 report, which highlights the vigorous activity in breast research in Manchester that has an overall goal of improving outcomes for breast cancer patients across the world.

Professor Rob Clarke
Director, Manchester Breast Centre

Manchester Breast Centre
From Molecular Science to the Clinic

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MANCHESTER CANCER RESEARCH CENTRE

IMPACT OF MANCHESTER BREAST CENTRE RESEARCH ON WOMEN AT HIGH RISK OF BREAST CANCER

Tony Howell, founder of the Family History Clinic

In the 1980s, the rising incidence of breast cancer (BC) and the introduction in the UK of the NHS National Health Service Breast Screening Programme (NHSBSP) led women with a family history of the disease to seek advice concerning management of their personal risk.

In response to concerns expressed by primary care physicians and colleagues within our breast oncology service, Tony Howell established a referral Family History Clinic (FHC) in Manchester, UK, in 1987 with a cancer genetics service initiated by Gareth Evans in 1990 (1). The aims of the FHC were to introduce a service for the estimation and management of breast cancer risk by initiating screening and prevention for women with familial risk and to evaluate the short- and long-term effectiveness of the clinic (Figure 1). Here we outline some of the important recent advances from our collaborative studies.

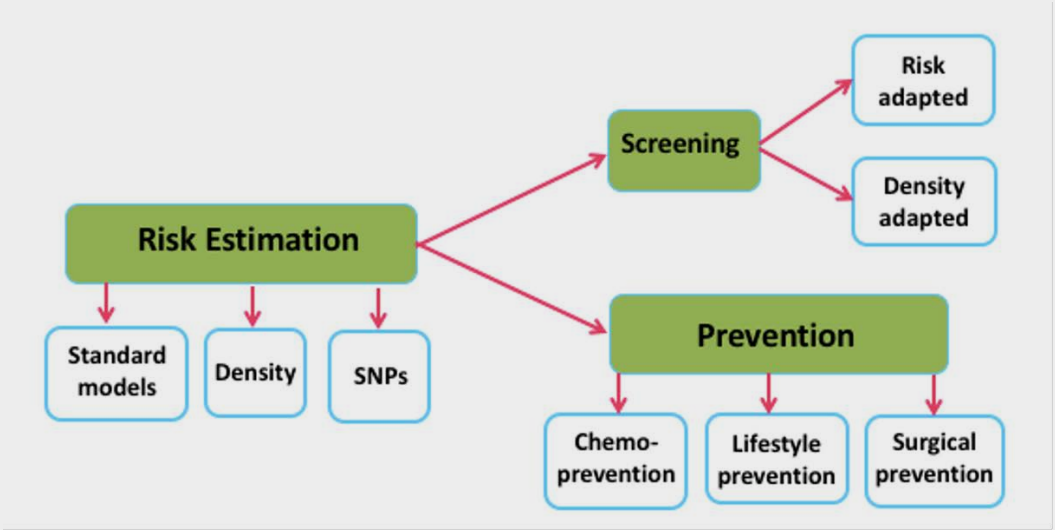


Figure 1. The aim of the clinic is to optimise risk estimation, screening and prevention of breast cancer.

We recognised the importance of breast cancer risk estimation at the beginning of the service and our models to determine risk have evolved over time. Currently we use an update of the model introduced by our collaborator Professor Jack Cuzick (The Tyrer-Cuzick model. 2004) in which family history is combined with other risk factors such as age of menarche, age of first full term pregnancy and menopause and the use of HRT. We assessed this model in a population of over 57,000 women in the National Health Service Breast Screening Programme in Greater Manchester based on the Nightingale Breast Screening Centre at Wythenshawe (The PROCAS Study: Prediction of Breast Cancer at Screening) led by Gareth Evans (Evans 2016. Details of all references may be found in the reference at the end of this section. Howell A et al). In this study we assessed the additional value of incorporating mammographic density (MD) and breast cancer risk associated single nucleotide polymorphisms (SNPs) in a polygenic risk score (PRS) to the standard Tyrer-Cuzick model (Figure 2).

More women were found to be in the high and low risk groups when MD and SNPs are added to the model. An important observation was that the high-risk cancers tended to occur in the high risk groups (Figure 2. Evans 2019).

These observations lead to the suggestion that breast screening should be adapted to breast cancer risk rather than a standard screening interval for all. We are part of a recently initiated European randomised trial of standard versus risk adapted breast screening (MyPebs. My Personal Breast Screening). Also we need to assess whether initiating screening and prevention at a young age will improve outcome so Sacha Howell and Sue Astley are leading on a trial using risk estimation and low dose mammograms in women under 40.

It is important to detect women who carry mutations (now called 'pathological variants') in the known breast cancer genes such as *BRCA1* and *BRCA2*, mainly found in women with a strong family history of breast cancer. Testing for these genes became available soon after their discovery in in the mid 1990's. In our review of all women referred to the Manchester Family History Clinic (1) we found that approximately 6% of referred women carried PVs, mainly in *BRCA1* and *BRCA2* but also *PALB2*, *CHEK2* and *ATM* (Dorling 2020). Thus, although it is important to detect and treat carriers appropriately it is clear that only a minority of women with a family history carry PVs.

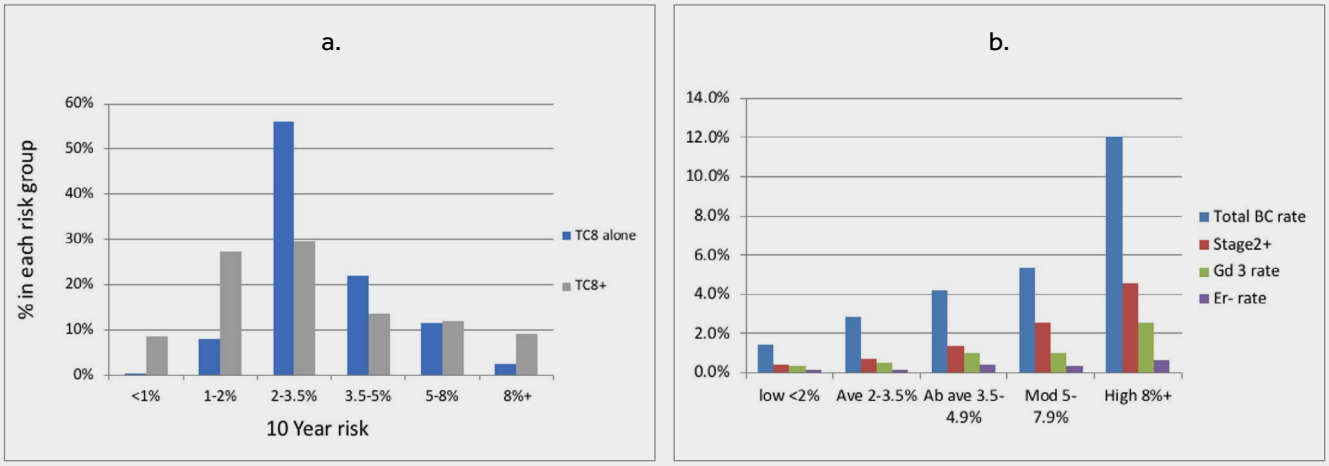


Figure 2. a. Distribution of 10-year risk of breast cancer estimated using the standard Tyrer-Cuzick model without (TC8) or with mammographic density and PRS (TC+) indicating an increase in the proportion of women at high and low risk in the extended model. b. The proportion of women with high risk tumours (stage 2a+, tumours >/= 2cm or more high grade and oestrogen receptor-ve [ER-ve]) increases related to percent ten year risk.

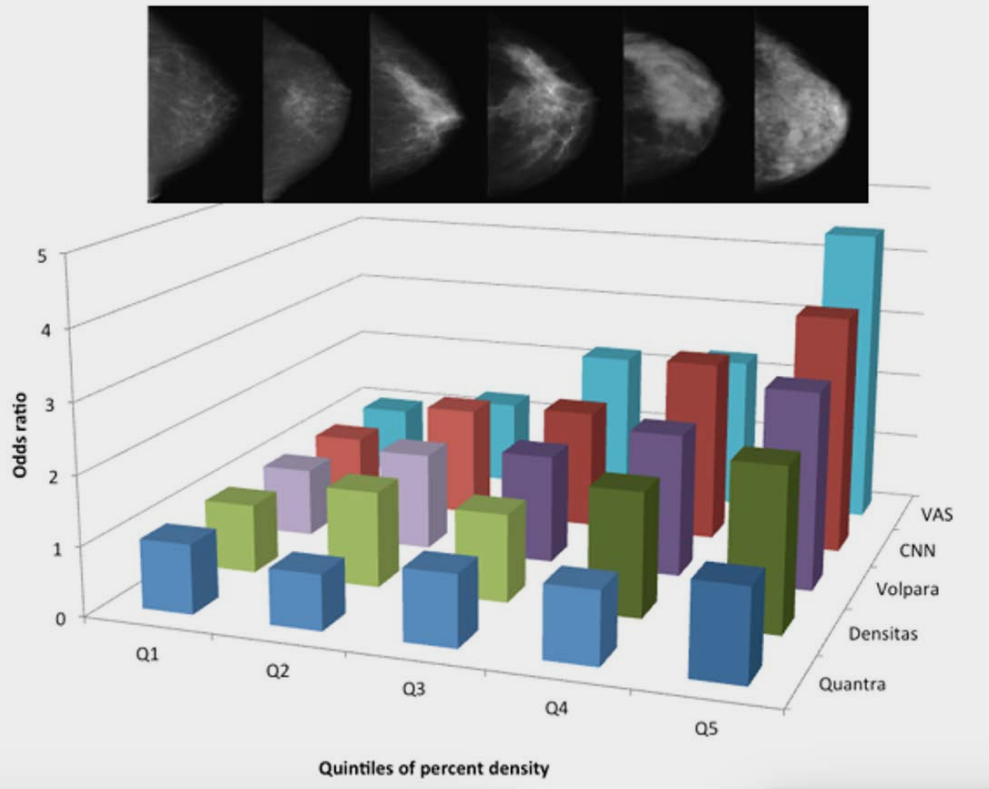


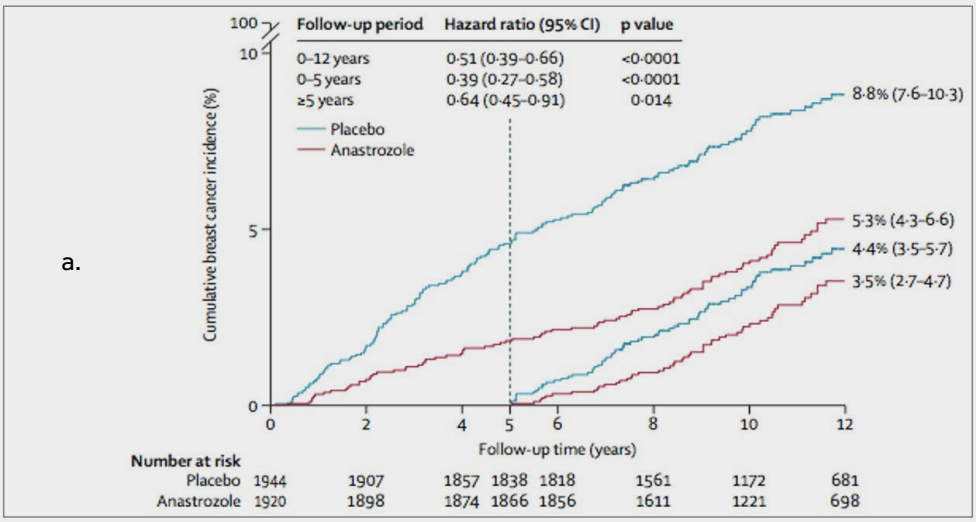
Figure 3. Automating breast density evaluation. In the PROCAS study we demonstrated that radiologist estimation of density using a visual analogue scale (VAS) was superior to other techniques. Importantly, Dr Astley, using convoluted neural networks (CNN), has shown that this automatic techniques gives similar results to VAS. The range of breast cancer density is also shown.

Although family history is the major reason for referral to the clinic, our studies in PROCAS indicate that not only were 20% of women at high and moderately high risk, but that about half of these did not have a family history of the disease. Others may have risk related to the sum of the density of their breasts, their SNP profile and hormonal risk factors. A major challenge now is to detect the whole at-risk population in order to offer screening and preventive measures appropriately.

In two studies led from Manchester and two national studies we have demonstrated that annual screening in the FHC by annual mammography (with additional MRI in the very high risk) results in improvements in survival after breast cancer compared with no screening (Leach 2005, Maurice 2006, Duffy 2010, Evans 2019). Screening is also important since it allows estimation of mammographic density. The challenge here is to determine the proportion of dense tissue in the breast automatically. Sue Astley and her team have shown recently that a method of density estimation based on AI is as good as radiologist estimation and this is likely to be the major method for automatic density determination in the future (Ionescu 2019. Figure 3).

We use risk estimation not only to offer screening but also preventive measures including lifestyle change, preventive therapy and, in the highest risk women, risk reducing mastectomy (RRM). Although overweight and obesity were known to increase breast cancer risk, Michelle Harvie, who heads our Lifestyle Programme was one of the first to demonstrate that weight reduction decreased breast cancer risk (Harvie 2005). She went on to develop the two day diet (2 days of 50 – 60% energy restriction and 5 days of healthy eating) which offers an acceptable intervention for achieving weight reduction (Harvie 2013). More recently she has completed a randomised trial which

a.



b.

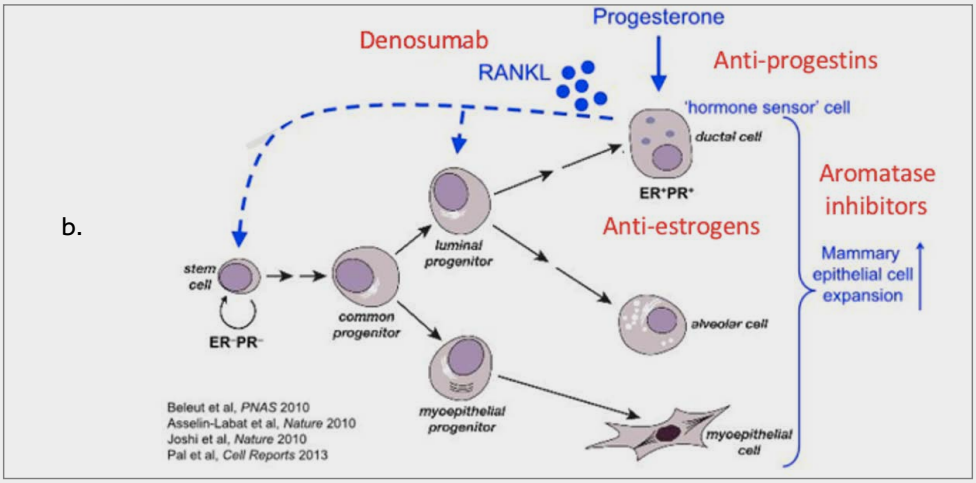


Figure 4 a. Cumulative incidence for all breast cancer by treatment allocation and follow-up period after 5 years of preventative anastrozole versus placebo. b. Differentiation pathway in the normal breast. Luminal progenitors give rise ductal cell which contain estrogen receptors (ER) and progesterone receptors (PR) the targets for preventive therapy. Alveolar cells produce and myoepithelial cells extrude milk during lactation.

has shown a remotely delivered (web and phone) weight loss programme is highly effective and will help us deliver lifestyle change more easily in the clinic (2020).

The mainstays of preventive therapy (chemoprevention) are tamoxifen for premenopausal women and raloxifene and anastrozole for postmenopausal women. Risk of breast cancer is reduced by 40-50% after five years use. Long term follow up of our trials show that tamoxifen remains effective for at least fifteen years and anastrozole (Figure 4a) for 10 years after completion of five years treatment (Cuzick 2015, Cuzick 2020). About 10% of women wish to be treated, a major problem being the misconception amongst of the side effect profiles. Recent studies indicate that the progesterone pathway is an important risk factor for breast cancer and studies are underway to test PR pathway inhibition with anti-progestins and denosumab (Figure 4b). These agents also have or are likely to have fewer side effects.

Breast cancer prevention by risk reducing surgery was introduced into our programme in 1995 and continues but with improvements in management and the introduction of newer surgical techniques. Women with BRCA1/2 PVs have up to an 85% risk of breast cancer and about half wish to undergo RRM. Approximately 5% of women with lower risk wish to undergo surgery. In Cox regression analyses, factors which independently predicted risk-reducing mastectomy uptake included either the death of a sister with BC <50 years or mother <60 years, having children, having a breast biopsy or younger age at assessment (<30 years). An update of all operations (n=451) indicates a risk reduction of 95.8% (1). The number of referrals for RRM were increased after Angelina Jolie indicated that she tested +ve for BRCA1 and had RRM (Figure 5. Evans 2014, 2015). The Breast Unit is fortunate in having not only excellent reconstructive surgeons but also with a great interest in improving cosmetic results. (Gandhi 2013, Dave 2020).

Our studies indicate that we have made improvements in risk estimation gene testing, screening, lifestyle, prevention, preventive therapy and RRM. However, major problems remain to be solved. These include how detect the majority women at high risk, how to offer genetic testing more appropriately, whether risk adapted screening is effective and how to increase uptake of lifestyle change and preventive measures[1].

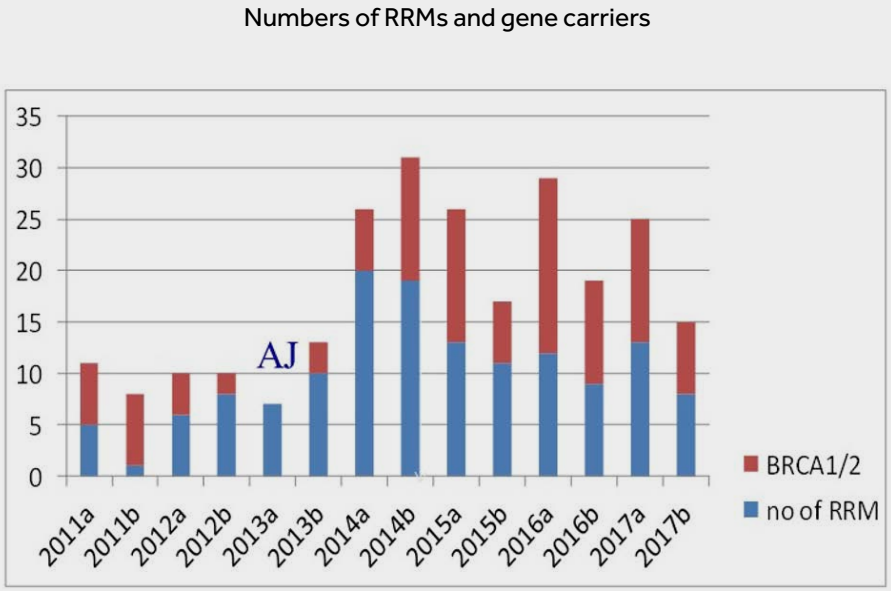


Figure 5. Numbers of risk reducing mastectomies per year in the Nightingale Breast Unit. These increased markedly after Angelina Jolie (see AJ 2013a) wrote about her *BRCA1* diagnosis. Red indicates number of operations in *BRCA1/2* carriers and blue in high risk non-carriers.

1. Howell A, Gandhi A, Howell SJ, Wilson M, Maxwell A, Astley S, Harvie M, Pegington M, Barr L, Baildam A, Harkness E, Hopwood P, Wisely J , Wilding A, Greenhalgh R, Affen J, Maurice A, Cole S, Wiseman J, Lalloo F, French DP, Evans DG. Long term evaluation of women referred to a Breast Cancer Family History Clinic (Manchester UK 1987-2020) Cancers 2020,12,3697; https://doi.org/10.3390/CANCERS12123697.

THE RESEARCH OF THE MANCHESTER BREAST CENTRE COMPRISES **4 INTER-RELATED AREAS**

There is a high degree of collaboration between the 21 Principal Investigators which enhances the research outcomes and translation to the clinic, and benefits patients. In the following pages, we highlight the Principal Investigators' research on each of the following topics – Laboratory, Risk and Prevention, Surgery and Oncology.

In addition, we have 16 Associate Members:

> **Pathology:** Sue Pritchard, Roger Hunt and Nisha Ali

> **Surgery:** Mohammed Absar and Kate Williams

> **Medical Physics:** Marianne Aznar

> **Biology:** Nancy Papalopulu, Kaye Williams, Sam Butterworth, Chiara Francavilla, Mike Sherratt, Sarah Woolner, Katie Finegan, Cathy Tournier, Jamie Honeychurch and Santiago Zelenay.

RESEARCH REPORTS

LABORATORY – STEM CELLS, METASTASIS & CELL BIOLOGY

ROB CLARKE

Breast Biology – Development and cancer

Group members:

Kath Spence, BSc – Senior Scientific Officer

Rachel Eyre, PhD – Postdoctoral Research Associate

Bruno Simões, PhD – Postdoctoral Research Associate

Angélica Santiago Gómez, PhD – Postdoctoral Research Associate

Hannah Harrison, PhD – Postdoctoral Research Associate

Matthew Roberts, BSc – Bioinformatician

Nathan Hull, MSc – Research Assistant

Megan Thompson, MSc – PhD Student

Tom Kedward, MSc – PhD Student

Suad Alghamdi, MSc – PhD Student

Aoife Kilgallon, BSc – PhD Student

Balkese Alhamad, MSc – PhD Student

Joe Parsons, BSc – PhD Student

Mia Nuckhir, MSc – PhD Student

Casey Broadbent, MSc – PhD Student

Emma Blower, MBChB (Hons) and MRCS – Surgical Fellow and PhD Student

Helen Clarke, MBChB (Hons) and MRCS – Surgical Fellow and PhD Student

The major research interests of the group are breast development, where we focus on hormonal regulation of luminal progenitors and cancer where bone metastasis and endocrine resistance are major interests.

Recently, we established a role for the human bone microenvironment in promoting colonisation of breast cancer cells through secretion of interleukin 1 beta (IL1β). We showed that IL1β induces Wnt signalling in the cancer cells and that drives colony-forming activity using novel models of patient-derived bone marrow and breast cancer cells (Refs 1 & 2).

Our research on estrogen receptor-positive (ER+) breast cancer aims to identify drivers of resistance to current standard of care treatments including endocrine and CDK4/6 inhibitor therapies. We previously established that ALDH+ cancer stem cells (CSCs) were responsible for anti-estrogen resistance driven by Notch4 receptor signalling (Simoes et al., Cell Reports, 2015), and more recently have shown that this is inhibited by peptides derived from FKBPL protein (3). We also exploited patient-derived samples from endocrine resistant patients to demonstrate a role for PAK4 kinase in resistance and validated the efficacy of a potent kinase inhibitor currently licenced by Cancer Research UK Commercial Partnerships (4). In exciting work published in Oncogene (5), we showed that endocrine resistant ALDH+ CSCs from patients could be inhibited by a stabilised formulation of sulforaphane (SFX-01). This research led from 'bench to bedside' providing the basis for the clinical trial (STEM01) in metastatic breast cancer led

by MBC Medical Oncologist Sacha Howell. Finally, we used single cell gene expression analysis of endocrine resistant CSCs to establish that there is a dormant population of cells remaining after treatment that are dependent on the IL1β signalling pathway (6). This links to our work in bone metastasis outlined above which indicates that endocrine resistant CSCs will respond to the bone microenvironment and may be sensitive to IL1β inhibitors such as Anakinra and Canakinumab. We hope our MBC clinical colleagues will test this in future clinical trials.

Highlighted papers 2019-2020

1. Eyre R, Alférez DG, Santiago-Gómez A, Spence K, McConnell JC, Hart C, Simões BM, Lefley D, Tulotta C, Storer J, Gurney A, Clarke N, Brown MD, Howell SJ, Sims AH, Farnie G, Ottewell PD and Clarke RB. Microenvironmental IL1β promotes metastatic colonisation of breast cancer cells in the bone via activation of Wnt signalling.
Nature Communications. 2019 Nov 1;10(1):5016
https://doi.org/10.1038/s41467-019-12807-0.

2. Lefley D, Howard F, Arshad F, Bradbury S, Brown H, Tulotta C, Eyre R, Alférez D, Wilkinson JM, Holen I, Clarke RB and Ottewell PD. Development of clinically relevant in vivo metastasis models using human bone discs and breast cancer patient-derived xenografts.
Breast Cancer Research. 2019 Nov 29;21(1):130.
https://doi.org/10.1186/s13058-019-1220-2.

3. McClements L, Annett S, Yakkundi A, O'Rourke M, Valentine A, Moustafa N, Alqudah A, Simões BM, Furlong F, Short A, McIntosh SA, McCarthy HO, Clarke RB and Robson T. FKBPL and its peptide derivatives inhibit cancer stem cells and breast cancer metastasis by down-regulating DLL4 and Notch4.
BMC Cancer. 2019 Apr 11;19(1):351.
https://doi.org/10.1186/s12885-019-5500-0.

4. Santiago-Gomez A, Kedward T, Simões BM, Dragoni I, NicAmhlaoibh R, Trivier E, Sabin V, Gee JM, Sims AH, Howell SJ and Clarke RB. PAK4 regulates stemness and progression in endocrine resistant ER-positive metastatic breast cancer.
Cancer Letters, 2019 Aug 28;458:66-75.
https://doi.org/10.1016/j.canlet.2019.05.014.

5. Lazaro-Carrillo A, Calero M, Aires A, Cortajarena AL, Simões BM, Latorre A, Somoza A, Clarke RB, Miranda R, Villanueva A. Tailored functionalized magnetic nanoparticles to target breast cáncer cells including cancer stem-like cells.
Cancers (Basel), 2020 May 29;12(6):E1397.
https://doi.org/10.3390/cancers12061397.

6. Simões BM, Santiago-Gómez A, Chiodo C, Moreira T, Conole D, Lovell S, Alferez D, Eyre R, Spence K, Sarmiento-Castro A, Kohler B, Morisset L, Lanzino M, Andò S, Marangoni E, Sims AH, Tate E, Howell SJ and Clarke RB. Targeting STAT3 signalling using stabilised sulforaphane (SFX-01) inhibits endocrine resistant stem-like cells in ER-positive breast cancer.
Oncogene. 2020 May 30.
https://doi.org/10.1038/s41388-020-1335-z.

7. Sarmiento-Castro A, Caamaño-Gutiérrez E, Sims AH, James MI, Santiago-Gómez A, Eyre R, Clark C, Brown ME, Brooks MD, Wicha MS, Howell SJ, Clarke RB* and Simões BM*. Increased expression of interleukin-1 receptor characterises anti-estrogen resistant ALDH+ breast cancer stem cells.
Stem Cell Reports. 2020 Aug 11;15(2):307-316.
https://doi.org/10.1016/j.stemcr.2020.06.020.
*Co-corresponding senior authors.

8. Woo et al., PDXNET consortium & EurOPDX consortium (Clarke RB). Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts.
Nature Genetics, 2020; 53(1):86-99.
https://doi.org/10.1038/s41588-020-00750-6.

9. Ashworth JC, Lis-Slimak K, Morgan RL, Jones S, Spence K, Slater CE, Thompson JL, Grabowska AM, Clarke RB, Farnie G and Merry CLR. A user-defined peptide gel for controlled 3D culture models of cancer and disease.
Journal of Visualized Experiments, 2020 Dec 3; (166).
https://doi.org/10.3791/61710.

AHMET UCAR

Stem cells in normal breast and breast tumours

Group members:

Fuhui Chen – PhD Student

Fiona He – Research Technician

The aim of our recently established research group is to better understand the cellular and microenvironmental mechanisms regulating the activity of stem cells in both normal breast and breast tumours.

Mammary epithelial stem cells (MaSCs) are at the apex of the cellular hierarchy of the breast epithelial cells, responsible for generating different types of cells required for the normal development and function of the breast. The intrinsic plasticity of the MaSCs ensures a lifetime production of new healthy cells to replenish the damaged cells as well as the rapid transformation of the breast during pregnancy, lactation and post-weaning involution. The defects that can occur in the MaSC plasticity may lead to the accumulation of genetic mutations and thus result in breast cancer. Our current research projects have recently revealed that different aspects of Rac1 signalling regulates the MaSC plasticity in murine mammary glands (manuscripts in preparation). Further elucidation of these mechanisms in the context of microenvironmental changes happening in the breast will allow us to better understand the normal breast biology as well as the earliest events underlying the formation of pre-malignant breast tumours.

Breast cancer stem cells (Br-CSCs) are a small population of cells within breast tumours that has similar features as MaSCs. They are the main driving force of the tumour progression, metastasis and treatment resistance. Our work has identified that Br-CSCs display a stem cell plasticity similar to the MaSCs, switching between quiescent and proliferative states under the regulation of the same Rac1- related molecular mechanisms (manuscripts in preparation). This suggests that Br-CSCs hijack the regulatory processes of normal MaSCs but modify the need of the microenvironmental controls on these processes. Our future work will aim to identify these microenvironmental checkpoints on stem cell plasticity with the hope that these can be therapeutically targeted in order to eradicate Br-CSC activities within breast tumours.

PAUL SHORE

Breast Cancer Metastasis: Molecular mechanisms

Group members:

Gabriel Velichkova – Research Technician

The main research area of the group is to understand the molecular basis for the development of specific metastatic phenotypes.

Our work focuses on the molecular mechanisms that determine changes in gene expression which subsequently enable disseminated breast cancer cells to colonise specific tissues. We have previously shown that the RUNX/CBFβ transcription factor complex drives the metastatic phenotype of some breast cancer cell types. More recently, we discovered that RUNX/CBFβ drives the epithelial to mesenchymal transition (EMT) of metastatic breast cancer cells (1). We demonstrated that CBFβ is essential to maintain the mesenchymal phenotype of triple-negative breast cancer cells and that CBFβ-depleted cells undergo a mesenchymal to epithelial transition (MET), and re-organise into acini-like structures, reminiscent of those formed by epithelial breast cells. We subsequently showed that the MET can be reversed, thus demonstrating the plasticity of CBFβ-mediated EMT. Importantly, the loss of CBFβ inhibits the ability of metastatic breast cancer cells to invade bone cell cultures and suppresses their ability to form bone metastases in vivo. Together our findings demonstrate that CBFβ can determine the plasticity of the metastatic cancer cell phenotype, suggesting that its regulation in different micro-environments may play a key role in the establishment of metastatic tumours.

In another study we showed that mutations in CBFβ contribute to the development of breast cancer by inducing a metastatic phenotype that is dependent on the estrogen receptor (ER) (2). CBFβ, the essential coregulator of RUNX transcription factors, is one of the most frequently mutated genes in estrogen receptor-positive (ER+) breast cancer. Recent work in our laboratory showed that many of these mutations accumulate near the Runt domain-binding region. These mutations inhibit the ability of CBFβ to form CBFβ-RUNX-DNA complexes. We further showed that deletion of CBFβ, using CRISPR-Cas9, in ER+ cells resulted in an increase in cell migration. This increase in migration is driven by the co-regulation of Trefoil Factor 1 (TFF1) by CBFβ and ERα. RUNX1/CBFβ acts to repress ERα-activated expression of TFF1. TFF1 is a motogen that stimulates migration and we show that knockdown of TFF1 in CBFβ-/- cells inhibits the migratory phenotype. Our findings reveal a new mechanism by which RUNX1-CBFβ and ERα combine to regulate gene expression and a new role for RUNX1-CBFβ in the prevention of cell migration by suppressing the expression of the motogen TFF1.

Highlighted papers 2019-2020

1. Ran R, Harrison H, Syamimi Ariffin N, Ayub R, Pegg HJ, Deng W, Mastro A, Ottewell PD, Mason SM, Blyth K, Holen I, Shore P. A role for CBFβ in maintaining the metastatic phenotype of breast cancer cells. Oncogene. 2020 Mar;39(12):2624-2637. https://doi.org/10.1038/s41388-020-1170-2.
2. Pegg HJ, Harrison H, Rogerson C, Shore P. The RUNX Transcriptional Coregulator, CBFβ, Suppresses Migration of ER+ Breast Cancer Cells by Repressing ERα-Mediated Expression of the Migratory Factor TFF1. Mol Cancer Res. 2019 May;17(5):1015-1023. https://doi.org/10.1158/1541-7786.MCR-18-1039.

ANDREW GILMORE

The extracellular matrix microenvironment and cell signalling

Group members:

Robert Pedley, PhD – Postdoctoral Research Associate

Eldhose Skaria, PhD - Postdoctoral Research Associate

Matthew Jones, BSc – PhD Student

Eliana Lingard, BSc – PhD Student

Simon Saadati, MSci – PhD Student

Alis Hales, MSc – PhD Student

Charlotte Mellor, MSci – PhD Student

We are interested in how changes in the extracellular matrix (ECM) microenvironment alter mammary epithelial cell function, and how this might lead to pro-oncogenic signalling and programmed cell death (apoptosis).

A key feature of the ECM is its mechanical stiffness. We are interested in how variations in this stiffness can promote mammary epithelial cell transformation. We have looked at how cells detect the properties of their microenvironment and transmit signals that change their behaviour, such as gene expression, differentiation and DNA damage. Using an in vitro culture model to recapitulate features of the mammary gland, we have examined the role of cytoskeletal proteins involved in mechano-sensing (2). Uncoupling adhesion to the ECM from mechano-sensing alters mammary cell gene expression to inhibit their differentiation. In collaborative work on cell response to mechanical load, links between forces applied to cells and DNA damage were identified (6). We are now looking at links between mechano-sensing and DNA damage in breast cancer initiation. Current studies are also defining the ECM components of breast tissue from women at high risk of cancer and incorporating these features into our culture system.

We have an active research interest in apoptosis, an important target for anticancer therapies (5). We are investigating how the central executioners of apoptosis, the Bcl-2 family of proteins, interact dynamically on mitochondria to set the threshold for the amount of stress that cells can endure before they die. Using live-cell imaging approaches to measure protein dynamics, we identified

that the rate of shuttling of key Bcl-2 proteins on and off mitochondria provides a dynamic control of this threshold (2). To understand how this shuttling is regulated, we have used a proximity labelling strategy coupled to mass-spectrometry. Using this, we identified novel Bcl-2 protein interactions that set the threshold for apoptosis in breast cancer cells treated with anti-mitotic drugs. We are now using this technique to look at how apoptosis is regulated in mammary epithelial cells in response to their ECM microenvironment.

Highlighted papers 2019-2020

1. Pedley R, King LE, Mallikarjun V, Wang P, Swift J, Brennan K, Gilmore AP. BioID-based proteomic analysis of the Bid interactome identifies novel proteins involved in cell-cycle-dependent apoptotic priming.
Cell Death Dis. 2020 Oct 16;11(10):872.
https://doi.org/10.1038/s41419-020-03091-8.

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J Biol Chem. 2020 Feb 7;295(6):1623-1636.
https://doi.org/10.1074/jbc.RA119.011635.

3. Wang P, Wu J, Wood A, Jones M, Pedley R, Li W, Ross RS, Ballestrem C, Gilmore AP, Streuli CH. Vinculins interaction with talin is essential for mammary epithelial differentiation.
Sci Rep. 2019 Dec 5;9(1):18400.
https://doi.org/10.1038/s41598-019-54784-w.

4. Atherton P, Lausecker F, Carisey A, Gilmore A, Critchley D, Barsukov I, Ballestrem C. Relief of talin autoinhibition triggers a force-independent association with vinculin.
J Cell Biol. 2020 Jan 6;219(1):e201903134.
https://doi.org/10.1083/jcb.201903134.

5. Gilmore A, King L. Emerging approaches to target mitochondrial apoptosis in cancer cells.
F1000Res. 2019 Oct 24;8:F1000 Faculty Rev-1793.
https://doi.org/10.12688/f1000research.18872.1.

6. Gilbert HTJ, Mallikarjun V, Dobre O, Jackson MR, Pedley R, Gilmore AP, Richardson SM, Swift J. Nuclear decoupling is part of a rapid protein-level cellular response to high-intensity mechanical loading.
Nature Communications. 2019 Sep 12;10(1):4149.
https://doi.org/10.1038/s41467-019-11923-1.

CHARLES STREULI

How breast cancer is caused by high mammographic density and by altered day-night clocks

Collaborators:

Charles is an emeritus professor and collaborates with **Andrew Gilmore** and **QingJun Meng**.

Mammographic density and breast cancer risk:

A central problem in cancer is that cell adhesion to the extracellular matrix changes, so the cells don't know how to behave properly.

High mammographic density is one of the greatest risk factors for breast cancer, and it correlates with a stiff tissue microenvironment. We are examining the way that this 'stiffness' contributes to cancer. Firstly, we are exploring how breasts with different mammographic densities are formed. Secondly, we are determining how the molecular architecture and protein/RNA/DNA composition differs between normal and tumour areas in women with different density breasts. Thirdly, we are examining how stromal stiffness causes genomic damage in breast epithelial cells, leading to an increased risk of cancer.

Circadian clocks in the breast:

Many breast genes are expressed under daily circadian cycles. We have found new links between the extracellular matrix and the control of these genes. For example, stiffening of the stromal matrix during ageing diminishes clock amplitude. These mechanical signals control clocks through a Rho-mediated pathway that links to gene expression. We have also discovered that circadian clocks are disrupted in early human breast cancers, and we are trying to find out how this contributes to the onset of the disease. We aim to determine whether restoring normal clocks in cancer cells can slow-down the progression of breast cancer.

Highlighted papers 2019-2020

1. Streuli CG, Meng QJ.
Influence of the extracellular matrix on cell-intrinsic circadian clocks.
J Cell Sci. 2019 Feb 1;132(3):jcs207498.
https://doi.org/10.1242/jcs.207498.

2. Wang P, Wu J, Wood A, Jones M, Pedley R, Li W, Ross RS, Ballestrem C, Gilmore AP*, Streuli CH*.
Vinculins interaction with talin is essential for mammary epithelial differentiation.
Sci Rep. 2019 Dec 5;9(1):18400.
https://doi.org/10.1038/s41598-019-54784-w.
(*Joint senior/contributing authors).

SANKARI NAGARAJAN

Translational Cancer Epigenetics

One of my postdoctoral research projects involved genome-wide CRISPR screens to understand drug resistance mechanisms to endocrine therapies in estrogen receptor-positive breast cancers.

My study revealed a novel role for the chromatin remodelling complex, the BAF complex, and its subunit ARID1A in controlling endocrine treatment response. My work emphasised the utilisation of BET inhibitors instead of standard endocrine therapies in patients harbouring mutations in ARID1A and other subunits of this complex. For this project, I had established genome wide CRISPR screens in the institute and exploited the platform for studying endocrine drug resistance. In addition, the work required developing ChIP-sequencing of BAF complex subunits which had previously proven to be intractable targets for the field. The work also involved ATAC-sequencing, Rapid Mass-spectrometry analysis of chromatin immunoprecipitated proteins (RIME) on clinical samples and ex vivo proliferation assays (explants) of patient-derived xenografts.

With my new research lab established in the Division of Molecular and Cellular Function, FBMH, I aim to study the role of epigenetic alterations and chromatin remodelling/ accessibility in driving drug resistance and metastasis in aggressive cancers such as breast, oesophageal, pancreatic and prostate cancers. I intend to employ single cell approaches to decipher the function of epigenetic reprogramming which can be represented in intratumour heterogeneity which leads to metastatic evolutionary trajectories developing as tumours in other secondary organs. These studies will help in the identification of molecular key drivers and transcription factors important for driving drug resistance and metastasis leading to poor outcome in patients.

Highlighted papers 2019-2020

1. Haider M-T, Saito H, Zarrer J, Uzhunnumpuram K, Nagarajan S, Kari V, Horn-Glander M, Werner S, Hesse E, and Taipaleenmäki H. Breast cancer bone metastases are attenuated in a Tgif1-deficient bone microenvironment.
Breast Cancer Research 2020 Apr 9;22(1):34.
https://doi.org/10.1186/s13058-020-01269-8.

2. Nagarajan S, Rao SV, Sutton J, Cheeseman D, Dunn S, Papachristou EK, Prada JG, Couturier DL, Kumar S, Kishore K, Chilamakuri CSR, Glont SE, Archer Goode E, Brodie C, Guppy N, Natrajan R, Bruna A, Caldas C, Russell A, Siersbæk R, Yusa K, Chernukhin I, Carroll JS. ARID1A influences HDAC1/BRD4 activity, intrinsic proliferative capacity and breast cancer treatment response.
Nat Genet. 2020 Feb;52(2):187-197.
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3. Siersbæk R, Scabia V, Nagarajan S, Chernukhin I, Papachristou EK, Broome R, Johnston SJ, Joosten SEP, Green AR, Kumar S, Jones J, Omarjee S, Alvarez-Fernandez R, Glont S, Aitken SJ, Kishore K, Cheeseman D, Rakha EA, D'Santos C, Zwart W, Russell A, Brisken C, Carroll JS. IL6/STAT3 Signaling Hijacks Estrogen Receptor α Enhancers to Drive Breast Cancer Metastasis.
Cancer Cell. 2020 Sep 14;38(3):412-423.e9.
https://doi.org/10.1016/j.ccell.2020.06.007.

4. Hossan, T., Kundu, S., Alam, S.S., and Nagarajan, S. (2019). Epigenetic Modifications Associated with the Pathogenesis of Type 2 Diabetes Mellitus. Endocr Metab Immune Disord Drug Targets 19, 775–786.

5. Holding AN, Giorgi FM, Donnelly A, Cullen AE, Nagarajan S, Selth LA and Markowetz F. VULCAN integrates ChIP-seq with patient-derived co-expression networks to identify GRHL2 as a key co-regulator of ERa at enhancers in breast cancer.
Genome Biol 2019 May 13;20(1):91.
https://doi.org/10.1186/s13059-019-1698-z.

KEITH BRENNAN

Regulation of cell behaviour during mammalian development

The complex development of multicellular organisms is regulated by surprisingly few signalling pathways that control cellular behaviours as diverse as adhesion, survival, migration, proliferation and fate determination.

We are interested in how so many diverse responses can be generated from so few pathways and how developmental signalling pathways regulate cell behaviour.

Highlighted papers 2019-2020

Pedley R, King LE, Mallikarjun V, Wang P, Swift J, Brennan K, Gilmore AP. BioID-based proteomic analysis of the Bid interactome identifies novel proteins involved in cell-cycle-dependent apoptotic priming. Cell Death Dis. 2020 Oct 16;11(10):872. https://doi.org/10.1038/s41419-020-03091-8.

RESEARCH REPORTS

RISK & PREVENTION – RISK ESTIMATION, SCREENING AND PREVENTION

GARETH EVANS

Genomic cancer risk stratification group

Collaborators and affiliated staff:

Dr Miriam Smith

Helen Byers

Dr Elaine Harkness

Dr Elke van Veen

Prof William Newman

Prof Tony Howell

Dr Sacha Howell

Dr Emma Woodward

2019-20 has seen the culmination of our work on risk stratification for breast cancer as part of the all Manchester NIHR Biomedical Research Centre Prevention Early Detection (PED) Theme [1-3].

We have contributed to a large number of high impact papers from our PROCAS and FHrisk cohorts [4,5]. We have published some important papers on long term follow up of chemoprevention trials [6], and on cost effectiveness of population BRCA testing for breast cancer [7]. A couple of papers on contralateral risk related to NF1 [8] and BRCA1, BRCA2 and TP53 have also been published [9]. We are hoping to expand our work on risk stratification with methylation work and have a number of gene panel papers in preparation.

Highlighted papers 2019-2020

1. Evans DGR, Harkness EF, ..Howell SJ, Maxwell AJ, Howell A, ... Newman WG, Cuzick J. Breast cancer pathology and stage are better predicted by risk stratification models that include mammographic density and common genetic variants.
Breast Cancer Res Treat. 2019 Apr 2.
https://doi.org/10.1007/s10549-019-05210-2.

2. Brentnall AR, ..., Astley SM,... Howell A, Newman WG, Cuzick J, Evans DGR. A case-control evaluation of 143 single nucleotide polymorphisms for breast cancer risk stratification with classical factors and mammographic density.
Int J Cancer. 2019 Jun 28.
https://doi.org/10.1002/ijc.32541.

3. Renehan A, Pegington M, Harvie M, Sperrin M, Astley S, Brentnall A, Howell A, Cuzick J, Evans DG. Young adulthood body mass index, adult weight gain and breast cancer risk: the PROCAS Study (United Kingdom).
Brit J Cancer 2020 Mar 23.
https://doi.org/10.1038/s41416-020-0807-9.

4. Fachal L, Aschard H, ...Evans DG, Howell A.. Kraft P, Dunning AM.(Multi-author) Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes.
Nat Genet. 2020 Jan;52(1):56-73.
https://doi.org/10.1038/s41588-019-0537-1.

5. Zhang H, Ahearn TU, ...Evans DG, Howell A.... Chatterjee N, García-Closas M.(Multi-author) Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses.
Nat Genet. 2020 May 18.
https://doi.org/10.1038/s41588-020-0609-2.

6. Cuzick J, Sestak I, Forbes JF, Dowsett M, Cawthorn S, Mansel RE, Loibl S, Bonanni B, Evans DG, Howell A. IBIS-II investigators Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial.
Lancet. 2020 Jan 11;395(10218):117-122.
https://doi.org/10.1016/S0140-6736(19)32955-1.

7. Sun L, Brentnall A, ..., Evans DGR, Eccles D, Hopper J, ...Manchanda R. A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer.
JAMA Oncol. 2019 Oct 3;5(12):1718-30.
https://doi.org/10.1001/jamaoncol.2019.3323.

8. Evans DGR, Kallionpää RA, Clementi M, Trevisson E, Mautner VF, Howell SJ, Lewis L, Zehou O, Peltonen S, Brunello A, Harkness EF, Wolkenstein P, Peltonen J. Breast cancer in neurofibromatosis 1: survival and risk of contralateral breast cancer in a five country cohort study.
Genet Med. 2019 Sep 9.
https://doi.org/10.1038/s41436-019-0651-6.

9. Hyder Z, Harkness EF, Woodward ER, Bowers NL, Pereira M, Wallace AJ, Howell SJ, Howell A, Lalloo F, Newman WG, Smith MJ, Evans DG. Risk of Contralateral Breast Cancer in Women with and without Pathogenic Variants in BRCA1, BRCA2, and TP53 Genes in Women with Very Early-Onset (<36 Years) Breast Cancer.
Cancers (Basel) 2020 Feb 7;12(2):378.
https://doi.org/10.3390/cancers12020378.

SUE ASTLEY

Breast Imaging

Group members:

Dr Steve Squires – Postdoctoral RA – AI

Dr Elaine Harkness – Postdoctoral RF – epidemiology

Ethan du Crow – PhD Student

Areej Aloufi – PhD Student

Reham Altokhais – PhD Student

Breast density, which is both a major risk factor for the development of breast cancer and a marker for the efficacy of mammography as a screening modality, is central to the research of our group, and a key component of the stratification process for risk-adapted screening (French 2020).

We are using Artificial Intelligence (AI) to develop methods for estimating breast density from mammograms. Our initial approach trained a convolutional neural network to predict density using the average of two expert readers' estimates (Ionescu 2019). This method performed better at predicting future risk of breast cancer in an independent case-control set of mammograms than the leading automated methods which primarily assess quantity of density, indicating that other more subtle features of the images such as the pattern and distribution of density may also be important in risk assessment. With Sacha Howell we have now extended the methodology to mammograms taken at a tenth of the usual x-ray dose, with promising results (Squires 2020).

We are also interested in the way in which radiologists interpret mammograms, and the potential impact of aids such as CAD (Computer-Aided Detection) systems. One concern in the evaluation of such technologies is the presence of a 'safety net' effect, whereby readers evaluated firstly with, then without a CAD system, might not complete a thorough initial search when they know they will re-read the case with prompts (du Crow 2019). Some recent CAD systems have interactive interfaces and incorporate overall image risk scores, so we have also used eye tracking to investigate the effect of these on reader behaviour (du Crow 2020).

In Saudi Arabia, a much higher proportion of breast cancers are detected at a late stage, and repeated screening is uncommon. Via an international collaboration we are investigating various aspects of breast imaging research in this population, including breast density (Aloufi 2020).

In current research we are aiming to use AI to predict women with difficult-to-interpret mammograms in which a cancer might be masked (hidden) by image regions which are dense or patterned. We are also commencing a collaborative research project with a group in Toronto that aims to predict risk from both MRI and mammography images, using temporal change as a marker.

Highlighted papers 2019-2020

1. Ionescu GV, Fergie M, Brentnall AR, Cuzick J,Evans DG, Astley SM. Prediction of reader estimates of mammographic density using convolutional neural networks.
J Med Imaging (Bellingham) 2019 Jul;6(3):031405.
https://doi.org/10.1117/1.JMI.6.3.031405.
2. Squires S, Ionescu G, ...Evans DG, Maxwell A, Howell S, Astley SM. Automatic density prediction in low dose mammography.
In 15th International Workshop on Breast Imaging (IWBI2020) 2020 May 22 (Vol. 11513, p. 115131D).
https://doi.org/10.1117/12.2564714.
International Society for Optics and Photonics.
3. Du-Crow E, Astley SM, Hulleman J. Is there a safety-net effect with computer-aided detection?
J Med Imaging (Bellingham) 2020 Mar;7(2):022405.
https://doi.org/10.1117/1.JMI.7.2.022405.
4. Du-Crow E, Astley SM, Hulleman J. Suspicious minds: effect of using a lesion likelihood score on reader behaviour with interactive mammographic CAD.
In 15th International Workshop on Breast Imaging (IWBI2020) 2020 May 22 (Vol. 11513, p. 115130Y).
https://doi.org/10.1117/12.2556472.
International Society for Optics and Photonics.
5. Aloufi AS, ...Harkness EF, Astley S. Breast density in Saudi Arabia: intra and inter reader variability in screening mammograms assessed visually using BI-RADS and visual analogue scales.
In: Medical Imaging 2020: Image Perception, Observer Performance, and Technology Assessment 2020 Mar 16 (Vol. 11316, p. 113160H).
https://doi.org/10.1117/12.2548758.
International Society for Optics and Photonics.

MICHELLE HARVIE

Diet and lifestyle and the prevention and management of breast cancer

Group members:

Mary Pegington – PhD Student Research Dietitian

Cheryl Lombardelli – Research Dietitian

Sarah McDiarmid – Research Dietitian

Avni Vyas – Research Dietitian

Kath Sellers – Research Programme Coordinator

Suzy Krizak – Clinical trials administrator

Prevention of Breast cancer

Overall aim

This programme aims to define the relationship between weight, weight gain and risk of breast cancer to identify who is at risk. Also, to identify the best way to introduce weight control / weight loss breast cancer prevention programmes amongst high-risk women.

An epidemiological study amongst 57,000 women in the PROCAS study identified that weight gain was associated with breast cancer amongst women with a recall BMI aged 20 < 23.4 kg/m2 [HR per SD: 1.31 (95% CIs: 1.21-1.42)]. However, there were no associations for women with a recall BMI aged 20 years of >23.4 kg/m2 (1).

The PROCAS lifestyle study demonstrated the feasibility of engaging high-risk women who attend breast screening with weight loss to reduce their risk of breast cancer (2). Also, that a remotely delivered (web and phone) programme can support women to achieve clinically significant weight loss to reduce their risk of breast cancer (2). 65% of women who started the programme lost >5% of their weight, a level previously associated with 20 – 40% reduced breast cancer. The Family History Lifestyle Study has just completed follow up (209 women) and has tested the efficacy of the phone and web programme amongst high-risk women attending a family history risk assessment clinic (3). We are also extending this work to examine the feasibility of implementing weight loss programmes to high-risk women who attend breast screening. Also, the potential to engage women who have a false positive mammogram (4).

Weight gain is a major common risk factor for the development of breast and 11 other cancers. Mary Pegington published a comprehensive review of the magnitude and timing of adult weight gain, the aetiology and potential interventions to prevent weight gain in young women (5). We are currently developing a weight gain prevention app for young women which will be tested in future randomised trials.

Weight control and lifestyle interventions after a diagnosis of breast cancer

This programme aims to develop and test weight control intervenions after diagnosis, and their effects on the toxicity and efficacy of treatments. The Breast and Healthy Eating after Diagnosis of Breast Cancer (B-AHEAD-1) study was published in 2019 (6). The B-AHEAD-2 has tested intermittent energy restricted diets during chemotherapy. We are planning to undertake future trials to test the synergersistic effects of intermittent energy retsriction combined with exercise and or other agents, e.g. sulphorophane on the efficacy of chemotherapy.

Highlighted papers 2019-2020

1. Renehan A, Pegington M, Harvie M, Sperrin M, Astley S, Brentnall A, Howell A, Cuzick J, Evans DG. Young adulthood body mass index, adult weight gain and breast cancer risk: the PROCAS Study (United Kingdom).
Brit J Cancer 2020 Mar 23.
https://doi.org/10.1038/s41416-020-0807-9.
2. Harvie M, Pegington M, French D, Cooper G, McDiarmid S, Howell A, Donnelly L, Ruane H, Sellers K, Foden P, Evans DG. Breast cancer risk status influences uptake, retention and efficacy of a weight loss programme amongst breast cancer screening attendees: two randomised controlled feasibility trials.
BMC Cancer. 2019 Dec 4;19(1):1089.
https://doi.org/10.1186/s12885-019-6279-8.
3. Harvie, French DP, Pegington M, Evans DGR, Howell A. Family History Lifestyle Study. ISRCTN registry [serial online] 2020; Accessed May 15, 2020.
4. Long H, Brooks JM, Harvie M, Maxwell A, French DP. How do women experience a false-positive test result from breast screening? A systematic review and thematic synthesis of qualitative studies.
Br J Cancer. 2019 Aug;121(4):351-358.
https://doi.org/10.1038/s41416-019-0524-4.
5. Pegington M, French DP, Harvie MN. Why young women gain weight: A narrative review of influencing factors and possible solutions.
Obes Rev 2020 May;21(5):e13002.
https://doi.org/10.1111/obr.13002.
6. Harvie M, Pegington M, McMullan D, Morris J, Howell S, Howell A. The effectiveness of home versus community-based weight control programmes initiated soon after breast cancer diagnosis: a randomised controlled trial.
Br J Cancer. 2019 Sep;121(6):443-454.
https://doi.org/10.1038/s41416-019-0522-6.

SACHA HOWELL

Therapeutic Prevention

Group members:

Bruno Simões, PhD – Postdoctoral Research Associate

Hannah Harrison, PhD – Postdoctoral Research Associate

Matthew Roberts, BSc – Bioinformatician

Helen Clarke, MBChB (Hons) – Gynaecology Fellow and PhD Student

Suad Alghamdi, MSc – PhD Student

Clinical team members:

Professor Gareth Evans

Professor Tony Howell

Dr Anthony Maxwell

Dr Sue Astley

In the Therapeutic Prevention theme we have two key goals:

1. To identify biomarkers that will predict benefit to existing preventive agents such as tamoxifen and anastrozole.
2. To develop novel preventive approaches for women resistant to these existing drugs who are at risk from more aggressive tumour subtypes.

We have established a clinical trial platform at the Nightingale Centre, Manchester to recruit women at increased risk of breast cancer into serial breast biopsy studies of existing and novel preventive agents. We are currently recruiting women due to start tamoxifen therapy and initial results suggest clustering of baseline transcriptional profiles could differentiate responsive vs non-responsive breast tissue. We have also recently completed a study funded by Breast Cancer Now to test the anti-progestin ulipristal acetate in this platform. The tissue samples have been subjected to live cell assays in addition to bulk and single cell RNAseq and proteomics and indicate an inhibition of the luminal progenitor subpopulation, the cell of origin of aggressive triple negative breast cancers. Additional studies are due to get underway in late 2020/early 2021, the first testing total diet replacement in women at risk of breast and endometrial cancer due to obesity and the second a RANKL antagonist denosumab in women that carry a BRCA1 mutation. All studies are linked to radiological and serological biomarker analyses through our collaborative radiology and basic science team and should facilitate the future development of predictive biomarkers of response to existing and novel breast cancer preventive therapies.

RESEARCH REPORTS

SURGERY – TRIALS & TECHNIQUES

CLIONA KIRWAN

Cancer and Thrombosis Group

Group members:

Emma Blower – PhD Student

Urvashi Singh – mRes Student

John Castle – Research Assistant

Hudhaifah Shaker, Hamish Clouston, Adam Rees – past PhD Students and current collaborators

It was recognised over 150 years ago that patients with cancer, including breast cancer, have an increased risk of developing clots in the legs (deep vein thrombosis) and clots in the lungs pulmonary embolism). Cancer uses processes that we also see in wound healing to help it grow and spread, for example clotting.

Our research aims to understand how cancer and wound healing processes, such as clotting, interact. The CHAMPion study (Cancer-induced Hypercoagulability as A Marker of Prognosis) has shown that markers of clotting are seen in breast cancer, particularly more aggressive subtypes. TuFClot (Tumour fragments and the clotting system in breast cancer) looked at tumour cells in the circulation of patients with advanced breast cancers and found that women who had cancer cells circulating in the blood, also had increased clotting in the blood, and a reduced survival.

The TIP Trial (Thrombin Inhibition Preoperatively in Early Breast Cancer) is looking at a blood thinning drug in women with breast cancer, where tumour tissue is collected at the time of their surgery, in women who have had 2 weeks of anti-clotting tablets. The cells are then grown in the laboratory to see the effects of the anticlotting drugs.

Highlighted papers 2019-2020

1. Shaker H, Bundred NJ, Landberg G, Pritchard SA, Albadry H, Nicholson SL, Harries LJ, Heah JYE, Castle J, Kirwan CC. Breast cancer stromal clotting activation (Tissue Factor and thrombin): A pre-invasive phenomena that is prognostic in invasion. Cancer Med. 2020 Mar;9(5):1768-1778. https://doi.org/10.1002/cam4.2748.
2. Kirwan CC, Descamps T, Castle J. Circulating tumour cells and hypercoagulability: a lethal relationship in metastatic breast cancer. Clin Transl Oncol . 2020 Jun;22(6):870-877. https://doi.org/10.1007/s12094-019-02197-6.
3. Castle J, Blower E, Bundred NJ, Harvey JR, Thachil J, Marshall A, Cox K, Cicconi S, Holcombe C, Palmieri C, Kirwan CC. Rivaroxaban compared to no treatment in ER-negative stage I-III early breast cancer patients (the TIP Trial): study protocol for a phase II preoperative window-of-opportunity study design randomised controlled trial. Trials. 2020 Aug 27;21(1):749. https://doi.org/10.1186/s13063-020-04675-7.

ASHU GANDHI

Treatment de-escalation/ risk reducing mastectomy/breast reconstruction surgery

There is a significant movement to de-escalate treatment where safe and appropriate to do so for breast cancer patients. This is in recognition of the long-term morbidity that is associated with some forms of breast cancer therapy.

As overall and breast cancer specific survival has increased the issue of survivorship and quality of life assumes even greater importance. These guidelines were written as a multidisciplinary project involving all the main clinical groups involved in managing the care of women with breast cancer. They represent the distillation of best available evidence and serve as guidance for MDTs throughout the UK.

We have assessed the uptake and surgical outcomes of risk reducing mastectomy in women referred with a family history of breast cancer. In recent years, with the increasing appreciation of patient reported outcome measures in women undergoing risk reducing surgery, we sought more aesthetically focussed reconstruction options whilst not compromising risk reduction principles. This has allowed the safe introduction of skin sparing and nipple sparing mastectomy and autologous reconstruction with deep inferior epigastric perforator flaps or single stage prepectoral implant-based reconstruction. The use of acellular dermal matrices has revolutionised implant-based reconstruction allowing structural support of implants within a reconstruction to mimic natural breast ptosis. Further improvements may come from the use of lipomodelling to improve aesthetics and thus patient satisfaction.

Acellular dermal matrixes (ADMs) have revolutionised implant-based breast reconstruction during the last decade or so, facilitating direct-to-implant reconstruction, acting as a hammock to allow more natural ptosis and definition of the inframammary fold. They have many advantages and can be used in a spectrum of surgeries including both pre-pectoral and dual-plane re- constructions.

Highlighted papers 2019-2020

1. Gandhi A, Coles C, Makris A, Provenzano E, Goyal A, Maxwell AJ, Doughty J.
Axillary Surgery Following Neoadjuvant Chemotherapy - Multidisciplinary Guidance from the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology.
Clin Oncol (R Coll Radiol). 2019 Sep;31(9):664-668.
https://doi.org/10.1016/j.clon.2019.05.021.

2. Howell A, Gandhi A, Howell SJ, Wilson M, Maxwell A, Astley S, Harvie M, Pegington M, Barr L, Baildam A, Harkness E, Hopwood P, Wisely J , Wilding A, Greenhalgh R, Affen J, Maurice A, Cole S, Wiseman J, Lalloo F, French DP, Evans DG. Long term evaluation of women referred to a Breast Cancer Family History Clinic (Manchester UK 1987-2020)
Cancers 2020,12,3697;
https://doi.org/10.3390/CANCERS12123697.

3. Fakim B, Highton L, Gandhi A, Johnson R, Murphy J.
Implant-based breast reconstruction with Artia™ tissue matrix.
J Plast Reconstr Aesthet Surg. 2019 Sep;72(9):1548-1554.
https://doi.org/10.1016/j.bjps.2019.05.024.

JAMES HARVEY

Breast reconstructive surgery, Breast surgery devices

Currently Chief Investigator for the National Ibranet study looking at new localisation devices which help surgeons to locate small breast cancers during surgery and lead for BROWSE study looking at long-term outcomes of Strattice and implant-based breast reconstruction.

Highlighted papers 2019-2020

1. Boundouki G, Wong JR, Hee S, Croghan N, Stocking K, Pieri A, Critchley A, Kirwan CC, Harvey JR. Comparing Long-Term Local Recurrence Rates of Surgical and Non-Surgical Management of Close Anterior Margins in Breast Conserving Surgery
Breast Cancer Res Treat 2019 Jul;176(2):311-319.
https://doi.org/10.1007/s10549-019-05242-8.
2. Zacharioudakis K, Down S, Bholah Z, Lee S, Khan T, Maxwell AJ, Howe M, Harvey J.
Is the future magnetic? Magseed localisation for non palpable breast cancer. A multi-centre non randomised control study.
Eur J Surg Oncol. 2019 Nov;45(11):2016-2021.
https://doi.org/10.1016/j.ejso.2019.06.035.
3. Dave RV, Vucicevic A, Highton L, Harvey JR, Johnson R, Kirwan CC, Murphy J. Medium term outcomes following immediate prepectoral implant-based breast reconstruction using a cellular dermal matrix
Br J Surg . 2020 Sep 29.
https://doi.org/10.1002/bjs.11964.
4. Somasundaram SK, Potter S, Elgammal S, Maxwell AJ, Sami AS, Down SK, Dave RV, Harvey J.
Impalpable breast lesion localisation, a logistical challenge: results of the UK iBRA-NET national practice questionnaire.
Breast Cancer Res Treat 2020 Sep 10.
https://doi.org/10.1007/s10549-020-05918-6.

RAJIV V DAVE

Reconstructive breast surgery – delivery and training Evaluation of breast surgery devices

Rajiv Dave has led, and been in the steering committee, of several national collaborative studies in breast and endocrine surgery (Thy3000, IBRA2, NeST, IBRAnet Localisation study, B-MaP-C) which have gathered data from >10,000 patients to date.

He is currently in steering committees involved in the development of other national collaborative studies (MARECA, DAMM, MAMMA), a qualitative study arm of the B-MaP-C study (RESTORE-C19). He is also the CI of an upcoming National IBRAnet study to evaluate a new breast surgical device to localise impalpable breast cancers.

He has been involved in breast surgery teaching and training in Kenya and is part of a taskforce involved in development of the country's cancer services, with an emphasis on developing research networks and collaboration.

Highlighted papers 2019-2020

1. Dave RV, Vucicevic A, Barrett E, Highton L, Johnson R, Kirwan CC, Harvey JR, Murphy J. Risk factors for complications and implant loss after prepectoral implant-based immediate breast reconstruction: medium-term outcomes in a prospective cohort. Br J Surg. 2020 Sep 29. https://doi.org/10.1002/bjs.11964.
2. Somasundaram SK, Potter S, Elgammal S, Maxwell AJ, Sami AS, Down SK, Dave RV, Harvey J. Impalpable breast lesion localisation, a logistical challenge: results of the UK iBRA-NET national practice questionnaire. Breast Cancer Res Treat 2020 Sep 10. https://doi.org/10.1007/s10549-020-05918-6.
3. Highton LR, Dave RV, Barnes NLP. Breast cancer surgery during the COVID-19 pandemic. Br J Surg. 2020 Jul 20:10.1002/bjs.11819. https://doi.org/10.1002/bjs.11819.
4. Courtney A, O'Connell R, Rattay T, Kim B, Cutress RI, Kirwan CC, Gandhi A, Fairbrother P, Sharma N, Cartlidge CWJ, Horgan K, McIntosh SA, Leff DR, Vidya R, Potter S, Holcombe C, Copson E, Coles CE, Dave RV. The B-MaP-C study: Breast cancer management pathways during the COVID-19 pandemic. Study protocol. Int J Surg Protoc. 2020;24:1-5. https://doi.org/10.1016/j.isjp.2020.07.003.

Surgical Oncology

NIGEL BUNDRED

Group members:

Nathan Hull, MSc – Research Assistant

Donna Watterson

Research into mechanisms and genetics of arm lymphoedema in a large 1200 multicentre UK study has continued and datalinkage to determine the effects of Body Mass Index, social deprivation and treatment into outcomes of lymphoedema and breast cancer are in progress.

Studies of the effect of margin involvement with cancer or DCIS after surgery include a large ongoing metaanalysis , work with the National Cancer Registry and a UK NIHR Trial.

Laboratory work is investigating the role of HER2 tyrosine Kinase Inhibition on Cancer Stem Cell Function.

Highlighted papers 2019-2020

1. Bundred N, Todd C, Morris J, Keeley V, Purushotham A, Bagust A, Foden P, Bramley M, Riches K. Individualising breast cancer treatment to improve survival and minimise complications in older women: a research programme including the PLACE RCT. Southampton (UK): NIHR Journals Library; 2019 Aug. PMID: 31436943.
2. Bundred N, Foden P, Todd C, Morris J, Watterson D, Purushotham A, Bramley M, Riches K, Hodgkiss T, Evans A, Skene A, Keeley V; Investigators of BEA/PLACE studies.Increases in arm volume predict lymphoedema and quality of life deficits after axillary surgery: a prospective cohort study. Br J Cancer. 2020 Jul;123(1):17-25. https://doi.org/10.1038/s41416-020-0844-4.
3. Bundred J, Michael S, Bowers S, Barnes N, Jauhari Y, Plant D, Maishman T, Cutress R, Holleczek B, Dodwell D, Bundred N. Do surgical margins matter after mastectomy? A systematic review. Eur J Surg Oncol. 2020 Dec;46(12):2185-2194. https://doi.org/10.1016/j.ejso.2020.08.015.
4. Bundred NJ, Dodwell D, Bundred JR, Cutress RI. Residual disease after mastectomy. Lancet Oncol. 2020 Nov;21(11):e499. https://doi.org/10.1016/S1470-2045(20)30542-8.

ONCOLOGY – NEW DRUG DEVELOPMENT & IMMUNOTHERAPY

ANNE ARMSTRONG

SACHA HOWELL

CIARA O'BRIEN

ANDREW WARDLEY

In 'New Drug Development' we have four PIs. All were consultants in medical oncology at The Christie NHS Foundation Trust in 2019 – 2020 and led clinical and translational research programmes*.

The goal of our work is to improve the treatment of women, and indeed men, with breast cancer through careful translation of basic research findings from the MBC and beyond into investigator led clinical trials. Where successful these trial treatments then become the standard of care for tomorrow. The four PIs have distinct interests in their research.

Dr Anne Armstrong leads a programme investigating approaches to enhance the effects of immunotherapy in early and advanced breast cancer, particularly triple negative breast cancer. She collaborates closely with Santiago Zeleny, a basic science PI in the MBC and has attracted grant funding from Breast Cancer Now to translate the preclinical findings into a phase II clinical trial, testing the addition of non-steroidal anti-inflammatory drugs to immunotherapy with PD-L1 inhibition. In addition, Anne has contributed to numerous industry studies, particularly in the field of triple negative breast cancer and immunotherapy (see refs).

Dr Sacha Howell has a special interest in endocrine therapy and in particular mechanisms of resistance and how they can be subverted. In the FAKTION study, instigated and led by Dr Howell, the length of time women with advanced breast cancer benefited from the endocrine drug fulvestrant was doubled with addition of the drug capivasertib, a selective Akt inhibitor, (Jones R et al 2020). Not only was the combination well tolerated but the women receiving it lived on average six months longer than those receiving fulvestrant alone. This study has led to a much larger phase 3 trial which is currently recruiting internationally and if successful will have changed the approach to breast cancer management. In addition, Dr Howell also works closely with the Breast Biology Group of Professor Rob Clarke and has translated the findings of the group into successful treatment trials, with publications expected in 2021.

Professor Andrew Wardley* is recognised internationally for his work in HER2 positive breast cancer. He has contributed to numerous industry studies of novel approaches to treatment of patients with early and advanced Her2 positive breast cancer. He contributed to trial design and management through trial steering committee and trial management group membership. Andrew is the current chair of the NCRI Breast Clinical Studies Group, driving the agenda of breast cancer clinical trials research nationally.

Dr Ciara O'Brien is an early career researcher with a keen interest in breast cancer metastasis. She works closely with Professor Rob Clarke's team to define mechanisms of metastasis that could be targeted in future clinical trials. This builds on Ciara's translational work in which she helped to define biomarkers to personalise early phase trial treatments through analysis of circulating tumour DNA (Rothwell DG et al 2019).

*Professor Andrew Wardley is no longer affiliated with The Christie NHS Foundation Trust.

Highlighted papers 2019-2020

1. Jones RH, Casbard A, Carucci M, Cox C, Butler R, Alchami F, Madden TA, Bale C, Bezecny P, Joffe J, Moon S, Twelves C, Venkitaraman R, Waters S, Foxley A, Howell SJ. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial.
Lancet Oncol. 2020 Mar;21(3):345-357.
https://doi.org/10.1016/S1470-2045(19)30817-4.

2. Rothwell DG, Ayub M, Cook N, Thistlethwaite F, Carter L, Dean E, Smith N, Villa S, Dransfield J, Clipson A, White D, Nessa K, Ferdous S, Howell M, Gupta A, Kilerci B, Mohan S, Frese K, Gulati S, Miller C, Jordan A, Eaton H, Hickson N, O'Brien C, Graham D, Kelly C, Aruketty S, Metcalf R, Chiramel J, Tinsley N, Vickers AJ, Kurup R, Frost H, Stevenson J, Southam S, Landers D, Wallace A, Marais R, Hughes AM, Brady G, Dive C, Krebs MG. Utility of ctDNA to support patient selection for early phase clinical trials: the TARGET study.
Nat Med. 2019 May;25(5):738-743.
https://doi.org/10.1038/s41591-019-0380-z.

3. Turner NC, Kingston B, Kilburn LS, Kernaghan S, Wardley AM, Macpherson IR, Baird RD, Roylance R, Stephens P, Oikonomidou O, Braybrooke JP, Tuthill M, Abraham J, Winter MC, Bye H, Hubank M, Gevensleben H, Cutts R, Snowdon C, Rea D, Cameron D, Shaaban A, Randle K, Martin S, Wilkinson K, Moretti L, Bliss JM, Ring A. Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial.
Lancet Oncol. 2020 Oct;21(10):1296-1308.
https://doi.org/10.1016/S1470-2045(20)30444-7.

4. Adams S, Loi S, Toppmeyer D, Cescon DW, De Laurentiis M, Nanda R, Winer EP, Mukai H, Tamura K, Armstrong A, Liu MC, Iwata H, Ryvo L, Wimberger P, Rugo HS, Tan AR, Jia L, Ding Y, Karantza V, Schmid P. Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study.
Ann Oncol. 2019 30 405-411.
https://doi.org/10.1093/annonc/mdy518.

5. Tolaney SM, Wardley AM, Zambelli S, Hilton JF, Troso-Sandoval TA, Ricci F, Im SA, Kim SB, Johnston SR, Chan A, Goel S, Catron K, Chapman SC, Price GL, Yang Z, Gainford MC, André F. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial.
Lancet Oncol. 2020 Jun;21(6):763-775.
https://doi.org/10.1016/S1470-2045(20)30112-1.

6. Earl HM, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L, Harnett AN, Ah-See ML, Simcock R, Rea D, Raj S, Woodings P, Harries M, Howe D, Raynes K, Higgins HB, Wilcox M, Plummer C, Mansi J, Gounaris I, Mahler-Araujo B, Provenzano E, Chhabra A, Abraham JE, Caldas C, Hall PS, McCabe C, Hulme C, Miles D, Wardley AM, Cameron DA, Dunn JA; PERSEPHONE Steering Committee and Trial Investigators. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial.
Lancet. 2019 Jun 29;393(10191):2599-2612.
https://doi.org/10.1016/S0140-6736(19)30650-6.

PUBLIC ENGAGEMENT

On 23 October 2020, to celebrate the Breast Cancer Awareness month and mark the 'Wear it Pink' day, Manchester Breast Centre organised its first ever virtual online Public Engagement event.

This event aimed to share with the public the current scientific knowledge on "How we can predict and prevent breast cancer now?". Four of our esteemed scientists, Professors Cliona Kirwan, Gareth Evans, Charles Streuli and Dr Sacha Howell, provided short talks explaining various issues around this topic such as: "How to self-examine breasts, what happens at a breast clinic", "how do we predict breast cancer risk and why is it important", "what type of clinical approaches can be used to prevent breast cancer for women with high risk of developing breast cancer", and "what are the benefits of breast-feeding in terms of breast cancer risk and prevention". These presentations were followed by a live Q&A session from our scientific panel answering questions received from the public in advance or during the event.

Watch the Virtual public outreach event YouTube

On the day of the event, we had over 100 attendees joining this live virtual event including members of public from the UK as well as from other countries such as Germany, Turkey and Kenya. The event was recorded and subsequently made available on YouTube and on the MBC homepage for the public and has been viewed several hundreds of times since. With highly encouraging feedback obtained from the attendees after the event, Manchester Breast Centre is planning to organise further virtual public outreach events in future in addition to our usual schedule of in-person public engagement events.

Dr Ahmet Ucar
Public Engagement Officer, Manchester Breast Centre

> *"How we can predict and prevent breast cancer now?"*

BREAST CANCER NOW-FUNDED MBC SEMINARS 2019-2020

Manchester Breast Centre
From Molecular Science to the Clinic

BREAST CANCER NOW The research & care charity

An important activity of the Manchester Breast Centre (MBC) is the monthly external seminar series, sponsored by Breast Cancer Now, which connects MBC researchers with the wider scientific community and fosters national and international collaborations.

We have enjoyed a very successful seminar series with an outstanding range of internationally renowned speakers visiting the centre in 2019 and delivering virtual seminars in 2020.

Breast Cancer Now also sponsors two internal seminar series events each year, which highlight the research of both senior scientists and trainees within the MBC. These are very well attended and help to integrate the entire breast cancer research efforts of the MBC.

External Seminars

Therese Sorlie
Oslo University Hospital, Norway

Cathrin Brisken
Swiss Federal Institute of Technology Lausanne, Switzerland

Jeff Pollard
University of Edinburgh

Zuzana Koledova
Masaryk University, Czech Republic

Hasan Korkaya
Augusta University, GA, USA

Maria del Mar Vivanco
CIC bioGUNE, Bilbao, Spain

Carla van Gils
University Medical Center, Utrecht

Karin de Visser
Netherlands Cancer Institute, The Netherlands

Cristina Branco
Queen's University Belfast

Charlotte Coles
Cambridge University Hospitals

Max Wicha
University of Michigan, USA

Martin Yaffe
University of Toronto, Canada

Geoff Lindeman
Walter and Elisa Hall Institute for Medical Research, Melbourne, Australia

Jeffrey Rosen
Baylor College of Medicine, Houston, USA

Internal Seminars

Talks from MBC Senior Scientists

Bruno Simões
Research Fellow, Breast Biology Group

Ahmet Ucar
Breast Cancer Now Fellow and Lecturer

Sacha Howell
Senior Lecturer, Medical Oncology

Anne Armstrong
Senior Lecturer, Medical Oncology

Andrew Gilmore
Senior Lecturer, Division of Cancer Sciences

Marianne Aznar
Senior Lecturer in Adaptive Radiotherapy

Sarah Woolner
Research Fellow, Wellcome Trust Centre for Cell Matrix Research

Angélica Santiago Gómez
Research Associate, Breast Biology Group

Sankari Nagarajan
Lecturer in Chromatin Biology, Division of Molecular & Cellular Function

CONFERENCES, SEMINARS AND PUBLIC EVENTS 2019-2020

Manchester Breast Centre Principal Investigators are much in demand at the national and international level to give seminars, conference lectures and to speak at public events.

Rob Clarke

Experimental Cancer Medicine Centre Showcase, OCRB, Manchester. 'Integrative Experimental Cancer Research at Manchester Breast Centre'. **18 January 2019**

Simposio Internacional de Biologia Molecular de Cancer, University of Guererro, Chilpancingo, Mexico. 'Regulation of breast cancer stem cell activity by the bone metastatic niche'. **10-11 April 2019**

International Association for Breast Cancer Research Conference, Amsterdam, The Netherlands. 'Microenvironmental IL1β promotes metastatic colonisation by breast cancer cells in the bone via activation of Wnt-dependent cancer stem cell activity'. **15-18 April 2019**

British Breast Group Summer Meeting, Sheffield. 'Microenvironmental IL1β promotes metastatic colonisation by breast cancer cells in the bone via activation of Wnt-dependent cancer stem cell activity'. **28 June 2019**

6th Annual Metastatic Breast Cancer Conference, Phoenix, AZ, USA. 'Regulation of Breast Cancer Stem Cell Activity by the Bone Metastatic Niche. **19-20 September 2019**

Ian MacKenzie Festshrift Conference, London. '1994-2019: 25 years of Cancer Stem Cells'. **23 October 2019**

Basel Breast Centre 4th Annual Meeting on Personalised Breast Cancer Medicine, Basel, Switzerland. 'Regulation of Breast Cancer Stem Cell Activity by the Bone Metastatic Niche'. **14-15 November 2019**

Institute of Cancer Therapeutics, University of Bradford. 'Regulation of breast cancer stem cell activity by the bone metastatic niche'. **14 February 2020**

Mellanby Centre, University of Sheffield. 'Regulation of breast cancer stem cell activity by the bone metastatic niche'. **1 May 2020**

Breast Cancer Research Symposium, University of Turku, Finland. 'Signalling pathways regulating endocrine resistance and metastasis in breast cancer'. **24 November 2020**

AACR Breast Cancer Symposium, San Antonio, TX, USA. 'Mechanisms of therapeutic resistance in ER+ breast cancer'. **8-11 December 2020**

Rajiv Dave

ABS Webinar. 'The impact on breast surgical units on COVID-19 and what we can learn from this'. **12 May 2020**

PanSurg Webinar. 'Management of Breast Cancer During the Covid-19 Pandemic'. **July 2020**

Towards building a structure for improved breast cancer care in Kenya - How can the UK help? 'Black women and breast cancer'. **October 2020**

NCRI Virtual Showcase. 'Cancer research and COVID-19: The impact on patients and professionals'. **October 2020**

UK-Kenya Global Health Partnerships for Resilient Health Systems – Diaspora Contribution. **2 December 2020**

Asian Society of Mastology Conference. 'Breast Cancer Management during the COVID-19 pandemic'. **6 December 2020**

Gareth Evans

Association of Breast Surgeons London. 'Breast cancer risk estimation with SNPs & BRCA related risks'. **January 2019**

Childhood Cancer Predisposition Symposium, Heidelberg. 'Gorlin syndrome and Neurofibromatsosis'. **January 2019**

Inherited Cancer symposium, Munich, Germany. 'BRCA related risks'. **January 2019**

Basser symposium, Philadelphia. 'Breast cancer genetic risk estimation'. **May 2019**

9th International Acoustic Neuroma and other CP angle tumour meeting, Rochester Minnesota. **June 2019**

BSGM, London. 'The BSGM lecture'. **October 2019**

NCRI conference, Glasgow. 'Risk stratification for breast cancer - does it work?'. **November 2019**

CTF NF conference. 'Neurofibromatosis 2'. **13-16 June 2020**

European Breast Cancer Conference. 'Gene panels'. **2-3 October 2020**

CR-UK Early detection conference - debate proposer 'All screening should involve genetic risk stratification' **7-8 October 2020**

Dutch HEBON meeting. 'PROCAS study'. **12 November 2020**

Mumbai all India cancer genetics conference. 'BRCA related cancer risks and NICE guidance'. **20 November 2020**

International ras meeting, Christie. 'NF1 cancer risks'. **8-9 December 2020**

Cancer Genetics Group. 'Changes to NHSBSP high risk screening'. **10 December 2020**

European Neurofibromatosis Conference on Schwannoma predisposing syndromes and public session, Rotterdam. 'NF2 and schwannomatosis'. **9-11 December 2020**

Sacha Howell

BreastFest: Prevent Breast Cancer Launch event, Manchester. **21 March 2019**

ASCO Chicago 'Capivasertib (AZD5363) plus fulvestrant versus placebo plus fulvestrant after relapse or progression on an aromatase inhibitor in metastatic ER-positive breast cancer (FAKTION): A randomized, double-blind, placebo-controlled, phase II trial'. **4 June 2019**

Shine Bright Charity annual away day, Manchester. 'Reducing the burden of breast cancer in our population and beyond. ' **13 September 2019**

Greater Manchester Cancer conference, Manchester. 'Reducing the Burden of Breast Cancer: Reaching the Unreached.' **20 November 2019**

Swedish Breast Group; Stockholm. 'The FAKTION trial and Breast Cancer prevention'. **24 January 2020**

First Thoughts conference; London. 'ER+ breast cancer – PI3K pathway and the Future Treatment Landscape'. **26 February 2020**

Tony Howell

Shanghai Breast Cancer Conference. 'Optimal Duration of Adjuvant Endocrine Therapy in Early Breast Cancer'. **2 March 2019**

University of Basel, Basel Breast Consortium Meeting, Switzerland. 'Risk adapted breast cancer screening and prevention'. **9 April 2019**

UK Imaging and Oncology Conference, Liverpool. 'Risk assessment in breast screening' in 'Personalised Breast Pathways'. **10 June 2019**

Georgian Cancer Study Group 6th Annual Symposium, Tbilisi. 'Genetics of Personalised Screening – Breast Density and Personalised Risk'. **12 October 2019**

Cliona Kirwan

Association of Breast Surgery Conference, Glasgow 2019: Overtreatment of DCIS. **13 May 2019**

Association of Breast Surgery Conference, Glasgow 2019: Surgical Management of DCIS during the Sloane Project. **14 May 2019**

NCRI National Breast Research Collaborative Meeting, 2019: Working Effectively as a Research Team, lessons from surgical studies. **13 September 2019**

Chair: UK Interdisciplinary Breast Cancer Symposium: Young Clinical Leaders. **28 January 2020**

UK Interdisciplinary Breast Cancer Symposium: Trainee collaborative research – a successful new story. **28 January 2020**

UK Interdisciplinary Breast Cancer Symposium: Academic Career Pathways. **28 January 2020**

Association of Breast Surgery Webinar (talk): Impact of Covid-19 on Academic Trainees. **19 May 2020**

Association of Breast Surgery Webinar (Chair): Personalised Breast Cancer Management. **4 August 2020**

Charles Streuli

Manchester Breast Centre Inaugural Think Tank. 'Breast Circadian Clocks are Altered in Breast Ageing and Cancer'. **15 February 2019**

Gordon Research Conference on Mammary Gland Biology, Newry, Maine. 'Mammographic Density and Circadian Clocks in Breast Cancer'. **9-14 June 2019**

European Network of Breast Development and Cancer, 4th Annual Think Tank Meeting, Manchester. Plenary talk: 'The future of breast development and cancer research – gaps and opportunities'. **12 December 2019**

Ahmet Ucar

BACR Newcastle meeting on Breast Cancer. 'Rac1b: A novel therapeutic target to eradicate breast cancer stem cells in luminal breast tumours'. **October 2019**

Gaziantep University, Turkey. 'Future directions in cancer research and therapeutics'. **December 2019**

Ashu Gandhi

Presentation: UK NHS BSP national audit data, Association of Breast Surgery Annual Scientific Conference (ABS) 2019.

Chair: Clinical Practice & Standards session ABS 2019: Owning your data.

Chair: Genetic Testing: Who and for what gene? ABS National Multidisciplinary Meeting 2019.

Presentation: Indications and pathways for risk reducing surgery ABS National Multidisciplinary Meeting 2019.

Chair: British Association of Endocrine & Thyroid Surgeons Annual Scientific Conference 2019: Free papers session.

Chair: British Association of Endocrine & Thyroid Surgeons Annual Scientific Conference 2019: Prize session.

Chair: ABS Webinar: Use of New Medical Devices 2020.

Presentation: Breast Screening during & after the Covid Pandemic ABS 2020.

FUNDING
MANCHESTER BREAST CENTRE RESEARCH

Our Principal Investigators receive charitable, commercial and governmental funding, which enables the basic, translational and clinical groups within the MBC to carry out their research.

We are immensely grateful to all our funding sources and in particular:

- Acelity
- Action Against Cancer
- Association of Breast Surgery
- Biotechnology and Biological Sciences Research Council (BBSRC)
- Boot Out Breast Cancer
- Breast Cancer Now
- Bupa UK Foundation
- Cancer Research UK (CRUK) Career Establishment Award
- Cancer Research UK (CRUK) International Alliance for Cancer Early Detection (ACED)
- Cancer Research UK (CRUK) Major Centre PhD Training Programme
- The Christie Charitable Fund
- European Union Horizon 2020
- Evgen
- Hologic
- Medical Research Council (MRC)
- National Institute for Health Research (NIHR)
- National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC)
- National Centre for the Replacement Refinement and Reduction of Animals in Research (NC3Rs)
- Prevent Breast Cancer
- Royal College of Surgeons England
- Shine Bright
- Tony Thornley
- Wellcome Trust

PUBLICATIONS
2019-2020

In 2019 and 2020, MBC researchers published 140 papers, of which more than 25% were published in highly respected journals with an impact factor of greater than 10. Our publications are all accessible by clicking on the hyperlinks in each of the references below.

1.0 Identification of new targets and therapies in the laboratory

1.1. Stem cells

Sarmiento-Castro A, Caamaño-Gutiérrez E, Sims AH, Hull NJ, James MI, Santiago-Gómez A, Eyre R, Clark C, Brown ME, Brooks MD, Wicha MS, Howell SJ, Clarke RB, Simões BM. Increased Expression of Interleukin-1 Receptor Characterizes Anti-estrogen-Resistant ALDH+ Breast Cancer Stem Cells.

Stem Cell Reports. 2020 Aug 11;15(2):307-316. https://doi.org/10.1016/j.stemcr.2020.06.020.

This paper establishes that anti-estrogen-resistant breast cancers have an increased interleukin-1 receptor-expressing cancer stem cell population and IL1R1 expression predicts anti-estrogen treatment failure.

Simões BM, Santiago-Gómez A, Chiodo C, Moreira T, Conole D, Lovell S, Alferez D, Eyre R, Spence K, Sarmiento-Castro A, Kohler B, Morisset L, Lanzino M, Andò S, Marangoni E, Sims AH, Tate EW, Howell SJ, Clarke RB. Targeting STAT3 signaling using stabilised sulforaphane (SFX-01) inhibits endocrine resistant stem-like cells in ER-positive breast cancer.

Oncogene. 2020 May 30. https://doi.org/10.1038/s41388-020-1335-z.

The data establish the importance of STAT3 signalling in CSC-mediated resistance to endocrine therapy and the potential of the drug SFX-01 for improving clinical outcomes in ER+ breast cancer.

Lazaro-Carrillo A, Calero M, Aires A, L Cortajarena A, Simões BM, Latorre A, Somoza Á, Clarke RB, Miranda R, Villanueva A. Tailored Functionalized Magnetic Nanoparticles to Target Breast Cancer Cells Including Cancer Stem-Like Cells.

Cancers (Basel), 2020 May 29;12(6):E1397. https://doi.org/10.3390/cancers12061397.

This study shows that nano formulations to be promising tools as therapeutic agent vehicles, due to their ability to produce efficient internalization and cancer cell inactivation, even in cancer stem-like cells (CSCs) from patients.

Garner KEL, Hull NJ, Sims AH, Lamb R, Clarke RB. The Milk Protein Alpha-Casein Suppresses Triple Negative Breast Cancer Stem Cell Activity Via STAT and HIF-1alpha Signalling Pathways in Breast Cancer Cells and Fibroblasts.

J Mammary Gland Biol Neoplasia. 2019 Sep;24(3):245-256. https://doi.org/10.1007/s10911-019-09435-1.

The data provide an explanation for the protective effects of lactation in TNBC. The milk protein alpha-casein was found to reduce breast cancer stem cell activity, and STAT3 and STAT1 were identified as regulators of pro-tumorigenic HIF-1alpha signalling in both breast cancer cells and fibroblasts.

Santiago-Gómez A, Kedward T, Simões BM, Dragoni I, NicAmhlaoibh R, Trivier E, Sabin V, Gee JM, Sims AH, Howell SJ, Clarke RB. PAK4 regulates stemness and progression in endocrine resistant ER-positive metastatic breast cancer.

Cancer Letters, 2019 Aug 28;458:66-75. https://doi.org/10.1016/j.canlet.2019.05.014.

This study establishes that PAK4 predicts for failure of endocrine therapies and poor prognosis and drives stemness and progression in ER + metastatic breast cancer. Targeting PAK4 abrogates breast CSC activity and restores sensitivity to endocrine treatments and will improve outcome of ER + breast cancer patients.

McClements L, Annett S, Yakkundi A, O'Rourke M, Valentine A, Moustafa N, Alqudah A, Simões BM, Furlong F, Short A, McIntosh SA, McCarthy HO, **Clarke RB**, Robson T.

FKBPL and its peptide derivatives inhibit endocrine therapy resistant cancer stem cells and breast cancer metastasis by downregulating DLL4 and Notch4.

BMC Cancer. 2019 Apr 11;19(1):351. https://doi.org/10.1186/s12885-019-5500-0.

This paper demonstrates the pre-clinical activity of novel systemic anti-cancer therapeutic peptides, ALM201 and AD-01, in the metastatic setting, and highlights their impact on endocrine therapy resistant CSCs.

1.2 Metastasis

Siersbæk R, Scabia V, **Nagarajan S**, Chernukhin I, Papachristou EK, Broome R, Johnston SJ, Joosten SEP, Green AR, Kumar S, Jones J, Omarjee S, Alvarez-Fernandez R, Glont S, Aitken SJ, Kishore K, Cheeseman D, Rakha EA, D'Santos C, Zwart W, Russell A, Brisken C, Carroll JS. IL6/STAT3 Signaling Hijacks Estrogen Receptor α Enhancers to Drive Breast Cancer Metastasis.

Cancer Cell. 2020 Sep 14;38(3):412-423.e9. https://doi.org/10.1016/j.ccell.2020.06.007.

The paper establishes that IL6 activates STAT3 which shares ER-FOXA1-STAT3 enhancers independent of FOXA1 and ER. The IL6/STAT3 signaling pathway then drives metastasis in ER+ breast cancer models.

Ran R, Harrison H, Syamimi Ariffin N, Ayub R, Pegg HJ, Deng W, Mastro A, Ottewell PD, Mason SM, Blyth K, Holen I, **Shore P**. A role for CBFβ in maintaining the metastatic phenotype of breast cancer cells.

Oncogene. 2020 Mar;39(12):2624-2637. https://doi.org/10.1038/s41388-020-1170-2.

The findings demonstrate that CBFβ can determine the plasticity of the metastatic cancer cell phenotype, suggesting that its regulation may play a key role in the establishment of metastatic tumours.

Haider M-T, Saito H, Zarrer J, Uzhunnumpuram K, **Nagarajan S**, Kari V, Horn-Glander M, Werner S, Hesse E, and Taipaleenmäki H. Breast cancer bone metastases are attenuated in a Tgif1-deficient bone microenvironment.

Breast Cancer Research 2020 Apr 9;22(1):34. https://doi.org/10.1186/s13058-020-01269-8.

This study demonstrates that lack of Tgif1 also restricts the progression of breast cancer bone metastases.

Peng F, Zhou Y, Wang J, Guo B, Wei Y, Deng H, Wu Z, Zhang C, Shi K, Li Y, Wang X, **Shore P**, Zhao S, Deng W.

The transcription factor Sp1 modulates RNA polymerase III gene transcription by controlling BRF1 and GTF3C2 expression in human cells.

J Biol Chem. 2020 Apr 3;295(14):4617-4630. https://doi.org/10.1074/jbc.RA119.011555.

These findings indicate that Sp1 controls Pol III-directed transcription and shed light on how Sp1 regulates cancer cell proliferation.

Lefley D, Howard F, Arshad F, Bradbury S, Brown H, Tulotta C, Eyre R, Alférez D, Wilkinson JM, Holen I, **Clarke RB**, Ottewell P. Development of clinically relevant in vivo metastasis models using human bone discs and breast cancer patient-derived xenografts.

Breast Cancer Research. 2019 Nov 29;21(1):130. https://doi.org/10.1186/s13058-019-1220-2.

These reliable and clinically relevant humanised mouse models provide significant advancements in modelling of breast cancer bone metastasis.

Eyre R, Alférez DG, Santiago-Gómez A, Spence K, McConnell JC, Hart C, Simões BM, Lefley D, Tulotta C, Storer J, Gurney A, Clarke N, Brown M, **Howell SJ**, Sims AH, Farnie G, Ottewell PD, **Clarke RB**. Microenvironmental IL1β promotes breast cancer metastatic colonisation in the bone via activation of Wnt signalling.

Nature Communications. 2019 Nov 1;10(1):5016. https://doi.org/10.1038/s41467-019-12807-0.

These findings establish that targeting IL1β-Wnt signalling should be considered for adjuvant therapy to prevent breast cancer bone metastasis.

Pegg HJ, Harrison H, Rogerson C, **Shore P**. The RUNX Transcriptional Coregulator, CBFβ, Suppresses Migration of ER+ Breast Cancer Cells by Repressing ERα-Mediated Expression of the Migratory Factor TFF1.

Mol Cancer Res. 2019 May;17(5):1015-1023. https://doi.org/10.1158/1541-7786.MCR-18-1039.

The data in this study suggest that mutations in CBFβ contribute to the development of breast cancer by inducing a metastatic phenotype that is dependent on ER.

1.3 Cell biology

Woo et al., PDXNET consortium & EurOPDX consortium (Clarke RB). Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts.

Nature Genetics, 2020; 53(1):86-99. https://doi.org/10.1038/s41588-020-00750-6.

Copy number alterations (CNAs) were analysed in 1451 patient-derived xenografts (PDX) and matched patient tumour (PT) samples and demonstrate strong genomic conservation from PTs through to late-passage PDX. This establishes the lack of systematic copy number evolution in PDX tumours and confirms that they are excellent models of patient tumours.

Ashworth JC, Lis-Slimak K, Morgan RL, Jones S, Spence K, Slater CE, Thompson JL, Grabowska AM, Clarke RB, Farnie G and Merry CLR. A user-defined peptide gel for controlled 3D culture models of cancer and disease.

Journal of Visualized Experiments, 2020 Dec 3; (166). https://doi.org/10.3791/61710.

The peptide hydrogel gel described here is free from matrix components and allows researchers to build a 3D culture environment that reflects the target tissue of interest. This enables them to independently dissect the influences of mechanical forces and the biochemical control of cell behaviour.

Atherton P, Lausecker F, Carisey A, Gilmore A, Critchley D, Barsukov I, Ballestrem C. Relief of talin autoinhibition triggers a force-independent association with vinculin.

J Cell Biol. 2020 Jan 6;219(1):e201903134. https://doi.org/10.1083/jcb.201903134.

How adhesion complexes form has been a controversial area for many years. This study indicated that, unlike the prevailing model, the key activation step for vinculin does not require acto-myosin dependent mechanical force.

Wang P, Wu J, Wood A, Jones M, Pedley R, Li W, Ross RS, Ballestrem C, Gilmore AP, Streuli CH. Vinculins interaction with talin is essential for mammary epithelial differentiation.

Sci Rep. 2019 Dec 5;9(1):18400. https://doi.org/10.1038/s41598-019-54784-w.

Discovery that the adhesion complex protein, vinculin, is essential for mammary epithelial cells to make milk. This novel function of vinculin is independent of its ability to bind to actin.

Gilbert HTJ, Mallikarjun V, Dobre O, Jackson MR, Pedley R, Gilmore AP, Richardson SM, Swift J. Nuclear decoupling is part of a rapid protein-level cellular response to high-intensity mechanical loading.

Nature Communications. 2019 Sep 12;10(1):4149. https://doi.org/10.1038/s41467-019-11923-1.

Tissues are often subject to high-intensity cyclical mechanical force. This paper shows that such mechanical loading results in uncoupling of the nucleus from the cytoskeleton, which acts to protect chromatin from damage.

Holding AN, Giorgi FM, Donnelly A, Cullen AE, Nagarajan S, Selth LA and Markowetz F. VULCAN integrates ChIP-seq with patient-derived co-expression networks to identify GRHL2 as a key co-regulator of ERa at enhancers in breast cancer.

Genome Biol 2019 May 13;20(1):91. https://doi.org/10.1186/s13059-019-1698-z.

The findings provide new insight into the role of GRHL2 in regulating eRNA transcription as part of estrogen receptor signalling.

Nagarajan S, Rao SV, Sutton J, Cheeseman D, Dunn S, Papachristou EK, Prada JG, Couturier DL, Kumar S, Kishore K, Chilamakuri CSR, Glont SE, Archer Goode E, Brodie C, Guppy N, Natrajan R, Bruna A, Caldas C, Russell A, Siersbæk R, Yusa K, Chernukhin I, Carroll JS. ARID1A influences HDAC1/BRD4 activity, intrinsic proliferative capacity and breast cancer treatment response.

Nat Genet. 2020 Feb;52(2):187-197. https://doi.org/10.1038/s41588-019-0541-5.

We describe ARID1A as a critical factor for response to estrogen receptor-alpha (ER) targeted drugs such as tamoxifen and fulvestrant. ARID1A mutations are more frequent in endocrine treatment-resistant disease, and the findings provide mechanistic insight into this process while revealing rational treatment strategies for these patients.

Streuli CH, Meng QJ.

Influence of the extracellular matrix on cell-intrinsic circadian clocks.

J Cell Sci. 2019 Feb 1;132(3):jcs207498. https://doi.org/10.1242/jcs.207498.

Review

Farcas AM, Nagarajan S, Cosulich S, Carroll JS. Genome-wide estrogen receptor activity in breast cancer.

Endocrinology. 2020 Dec 7: 162(2):bqaa224. https://doi.org/10.1210/endocr/bqaa224.

Review

Pedley R, King LE, Mallikarjun V, Wang P, Swift J, Brennan K, Gilmore AP. BioID-based proteomic analysis of the Bid interactome identifies novel proteins involved in cell-cycle-dependent apoptotic priming.

Cell Death Dis. 2020 Oct 16;11(10):872. https://doi.org/10.1038/s41419-020-03091-8.

Anti-mitotic drugs are a mainstay of breast cancer therapy. In this study we identified a key mechanism that sensitises breast cancer cells to anti-mitotic drugs involving the pro-apoptotic Bcl-2 protein, Bid, and the mitochondrial porin VDAC2.

Kuwana T, King LE, Cosentino K, Suess J, Garcia-Saez AJ, Gilmore AP, Newmeyer DD. Mitochondrial residence of the apoptosis inducer BAX is more important than BAX oligomerization in promoting membrane permeabilization.

J Biol Chem. 2020 Feb 7;295(6):1623-1636. https://doi.org/10.1074/jbc.RA119.011635.

Key steps in apoptosis include the recruitment of pro-apoptotic protein Bax to mitochondria where it oligomerises to form a pore, but the relative importance of each of these steps is unclear. This paper shows that it is the mitochondrial residency that is the critical step.

Gilmore A, King L. Emerging approaches to target mitochondrial apoptosis in cancer cells.

F1000Res. 2019 Oct 24;8:F1000 Faculty Rev-1793. https://doi.org/10.12688/f1000research.18872.1.

Review

Shaker H, Bundred NJ, Landberg G, Pritchard SA, Albadry H, Nicholson SL, Harries LJ, Heah JYE, Castle J, Kirwan CC. Breast cancer stromal clotting activation (Tissue Factor and thrombin): A pre-invasive phenomena that is prognostic in invasion.

Cancer Med. 2020 Mar;9(5):1768-1778. https://doi.org/10.1002/cam4.2748.

Rivaroxaban compared to no treatment in ER-negative stage I-III early breast cancer patients (the TIP Trial). This work provides the study design for a phase II preoperative window-of-opportunity randomised controlled trial.

Kirwan CC, Descamps T, Castle J.

Circulating tumour cells and hypercoagulability: a lethal relationship in metastatic breast cancer.

Clin Transl Oncol . 2020 Jun;22(6):870-877. https://doi.org/10.1007/s12094-019-02197-6.

Patients with metastatic breast cancer, increased blood coagulability, and evidence of circulating tumour cells, had significantly reduced survival.

2.0 Risk estimation, screening and prevention

Overview

Howell A, Gandhi A, Howell SJ, Wilson M, Maxwell A, Astley S, Harvie M, Pegington M, Barr L, Baildam A, Harkness E, Hopwood P, Wisely J , Wilding A, Greenhalgh R, Affen J, Maurice A, Cole S, Wiseman J, Lalloo F, French DP, Evans DG. Long term evaluation of women referred to a Breast Cancer Family History Clinic (Manchester UK 1987-2020)

Cancers 2020,12,3697; https://doi.org/10.3390/CANCERS12123697.

This report focusses on the evolution and improvements in risk estimation, genetic testing, screening and approaches to lifestyle, chemo and surgical prevention in the Manchester Family History Clinic from its inception in 1987.

2.1 Single nucleotide polymorphisms

Escala-Garcia M, Abraham J,.... Evans DG, Howell A..... Canisius S, Schmidt MK. (Multi-author) A network analysis to identify mediators of germline-driven differences in breast cancer prognosis.

Nature Communications. 2020 Jan 16;11(1):312. https://doi.org/10.1038/s41467-019-14100-6.

Aggregating the prognostic effects of genetic variants across multiple genes, identifies four gene modules associated with survival in estrogen receptor (ER)-negative and one in ER-positive disease. The modules show biological enrichment for cancer- related processes such as G-alpha signalling, circadian clock, angiogenesis, and Rho-GTPases in apoptosis.

Escala-Garcia M, Guo Q, ...**Evans DG**, **Howell A**... Pharoah PDP, Schmidt MK. (Multi-author)

Genome-wide association study of germline variants and breast cancer-specific mortality.

Br J Cancer 2019 Mar;120(6):647-657. https://doi.org/10.1038/s41416-019-0393-x.

This study shows little association between BC SNPs and mortality.

Mavaddat N, Michailidou K, ...**Evans DG**, **Howell A**... Simard J, Easton DF. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes.

Am J Hum Genet. 2019 Jan 3;104(1):21-34. https://doi.org/10.1016/j.ajhg.2018.11.002.

A polygenic risk score bases on 313 SNPs helps distinguish between risk of ER+ve and ER-ve disease.

Zhang H, Ahearn TU, ...**Evans DG**, **Howell A**.... Chatterjee N, García-Closas M.(Multi-author) Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses.

Nat Genet. 2020 May 18. https://doi.org/10.1038/s41588-020-0609-2.

This study helps define breast tumour subtype polygenic risk scores and gives some insight into the different mechanisms of development of each subtype.

Kapoor PM, Lindström S, Behrens S, ... García-Closas M, Easton DF, Milne RL, Chang-Claude J; (incl **Evans DG**) (Multi-author)

Assessment of interactions between 205 breast cancer susceptibility loci and 13 established risk factors in relation to breast cancer risk, in the Breast Cancer Association Consortium.

Int J Epidemiol. 2020 Feb 1;49(1):216-232. https://doi.org/10.1093/ije/dyz193.

Polygenic risk scores and classical risk factors may be combined multiplicatively. The greater the genetic risk the greater the additional effect of classical risk factors.

Kramer I, Hooning MJ, ...**Evans DG**, **Howell A**... Hall P, Schmidt MK. (Multi-author) Breast Cancer Polygenic Risk Score and Contralateral Breast Cancer Risk.

Am J Hum Genet. 2020 Sep 28:S0002-9297(20)30321-9. https://doi.org/10.1016/j.ajhg.2020.09.001.

PRS313 is an independent factor associated with CBC risk and can be incorporated into CBC risk prediction models to help improve stratification and optimize surveillance and treatment strategies.

Kapoor PM, Mavaddat N, ...**Evans DG**, **Howell A**.. García-Closas M, Chang-Claude J. (multi-author) Combined associations of a polygenic risk score and classical risk factors with breast cancer risk.

J Natl Cancer Inst. 2020 May 2:djaa056. https://doi.org/10.1093/jnci/djaa056.

The interactions between polygenic risk scores are multiplicative. The higher the PRS the greater the interaction.

Fachal L, Aschard H, ...**Evans DG**, **Howell A**.. Kraft P, Dunning AM.(Multi-author) Fine-mapping of 150 breast cancer risk regions identifies 191 likely target genes.

Nat Genet. 2020 Jan;52(1):56-73. https://doi.org/10.1038/s41588-019-0537-1.

Breast cancer risk variants are related to known cancer drivers, transcription factors and genes in the developmental, apoptosis, immune system and DNA integrity checkpoint gene ontology pathway.

Ferreira MA, Gamazon ER, ...**Evans DG**..... Beesley J, Chenevix-Trench G. (Multi-author) Genome-wide association and transcriptome studies identify target genes and risk loci for breast cancer.

Nat Commun. 2019 Apr 15;10(1):1741. https://doi.org/10.1038/s41467-018-08053-5.

In this study of GWAS of breast cancer, along with expression data from multiple different tissues, identifies 26 and 17 previously unreported likely target genes of known overall and ER-negative breast cancer risk variants, respectively.

Yang Y, Shu X, Shu XO, ... **Evans DGR**....Easton DF, Zheng W, Long J.

Re-evaluating genetic variants identified in candidate gene studies of breast cancer risk using data from nearly 280,000 women of Asian and European ancestry.

EBioMedicine . 2019 Oct;48:203-211. https://doi.org/10.1016/j.ebiom.2019.09.006.

Using a large amount of GWAS data, 14 variants in 10 candidate genes associated with breast cancer risk were discovered.

Pashayan N, Antoniou AC, Ivanus U, ... **Evans DG** ...Schmidt MK, Widschwendter M. Personalized early detection and prevention of breast cancer: ENVISION consensus statement.

Nat Rev Clin Oncol. 2020 Nov;17(11):687-705. https://doi.org/10.1038/s41571-020-0388-9.

Review

Barnes DR, Rookus MA, ..**Evans DG**, ...Faivre L, Antoniou AC; (Multi-author)Consortium of Investigators of Modifiers of BRCA and BRCA2. Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of BRCA1 and BRCA2 pathogenic variants.

Genet Med. 2020 Oct;22(10):1653-1666. https://doi.org/10.1038/s41436-020-0862-x.

Polygenic risk scores and other risk factors for breast or epithelial ovarian cancer influence the penetrance of BRCA1 and BRCA2 pathological variants.

2.2 Breast cancer genes and gene testing

Evans DG, Woodward ER, Bajalica-Lagercrantz S, Oliveira C, Frebourg T. Germline TP53 Testing in Breast Cancers: Why, When and How?

Cancers (Basel). 2020 Dec 14;12(12):3762. https://doi.org/10.3390/cancers12123762.

Germline TP53 variants represent a main genetic cause of breast cancers before 31 years of age. Development of cancer multi-gene panels has resulted in an exponential increase of germline TP53 testing in breast cancer patients. This paper indicates the variants in TP53 likely to be pathogenic.

Laitman Y, Michaelson-Cohen R, Chen-Shtoyerman R,... **Evans DG**....Paluch-Shimon S, Friedman E. Age at diagnosis of cancer in 185delAG BRCA1 mutation carriers of diverse ethnicities: tentative evidence for modifier factors.

Fam Cancer. 2020 Nov 9. https://doi.org/10.1007/s10689-020-00216-y.

Age at diagnosis of breast and ovarian cancer differs between Ashkenazi and Iraqi Jews who carry an identical BRCA1 pathogenic variants. This finding supports the existence of modifier factors that may be ethnic specific.

Evans DG, Woodward ER.

New surveillance guidelines for Li-Fraumeni and hereditary TP53 related cancer syndrome: implications for germline TP53 testing in breast cancer.

Fam Cancer. 2020 Sep 28. https://doi.org/10.1007/s10689-020-00207-z.

In children, the recommendations are to perform clinical examination and abdominal ultrasound every 6 months, annual WBMRI and brain MRI from the first year of life, if the TP53 variant is known to be associated with childhood cancers. In adults, the surveillance should include every year clinical examination, WBMRI, breast MRI in females from 20 until 65 years and brain MRI until 50 years.

Metcalfe KA, Price MA, Mansfield CA, Hallett DC, ... **Evans DG**, Narod SA, Liede A, Predictors of long-term cancer-related distress among female BRCA1 and BRCA2 mutation carriers without a cancer diagnosis: an international analysis.

Br J Cancer. 2020 Jul;123(2):268-274. https://doi.org/10.1038/s41416-020-0861-3.

Women with BRCA1/2 mutations indicated strong preferences for breast cancer risk reduction and maintaining fertility. The expressed desire to have a safe chemoprevention drug available to them was not met by current chemoprevention options.

Silvestri V, Leslie G, Barnes DR, ...**Evans DG**... Friedman E, Ottini L. (Multi-author)

Characterization of the Cancer Spectrum in Men With Germline BRCA1 and BRCA2 Pathogenic Variants: Results From the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). JAMA Oncol. 2020 Jul 2. https://doi.org/10.1001/jamaoncol.2020.2134.

Significant differences in the cancer spectrum were observed in male BRCA2, compared with BRCA1, PV carriers. These data may inform future recommendations for surveillance of BRCA1/2-associated cancers and guide future prospective studies for estimating cancer risks in men with BRCA1/2 PVs.

Hanson H, Brady AF, Crawford G, Eeles RA, ...Sohaib A, Tischkowitz M, **Evans DG**; Consensus Group Members UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants.

J Med Genet. 2020 Jun 22;58(2):135-139. https://doi.org/10.1136/jmedgenet-2020-106876.

The key recommendations are for annual WB-MRI and dedicated brain MRI from birth, annual breast MRI from 20 years in women and three-four monthly abdominal ultrasound in children along with review in a dedicated clinic.

Fortuno C, Mester J, ..., **Evans DG** ... Sandoval R; Li-Fraumeni Exploration (LIFE) Consortium, James PA, Spurdle AB. Suggested application of HER2+ breast tumor phenotype for germline TP53 variant classification within ACMG/AMP guidelines.

Hum Mutat. 2020 Jun 2. https://doi.org/10.1002/humu.24060.

These results show that the identification of HER2+ breast tumours diagnosed before the age of 40 can be conservatively incorporated into the current TP53-specific ACMG/AMP PP4 criterion, following a point system detailed in this manuscript.

Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheim R, **Evans DG**; European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes.

Eur J Hum Genet. 2020 Oct;28(10):1379-1386. https://doi.org/10.1038/s41431-020-0638-4.

In children, the recommendations are to perform clinical examination and abdominal ultrasound every 6 months, annual WBMRI and brain MRI from the first year of life, if the TP53 variant is known to be associated with childhood cancers. In adults, the surveillance should include every year clinical examination, WBMRI, breast MRI in females from 20 until 65 years and brain MRI until 50 years.

Forde C, Brunstrom K, Woodward E, ..., Lalloo F, Harkness EF, **Evans DG**. Uptake of pre-symptomatic testing for BRCA1 and BRCA2 is age, gender, offspring and time-dependent.

J Med Genet. 2020 Apr 30: jmedgenet-2019-106544. https://doi.org/10.1136/jmedgenet-2019-106544.

Uptake of BRCA1/2 pre-symptomatic testing is age, gender and time-dependent, and higher in women with children and men with daughters.

Garrett A, Callaway A, Durke M...Lalloo F, **Evans DG**,... Turnbull C; CanVIG-UK. Cancer Variant Interpretation Group UK (CanVIG-UK): an exemplar national subspecialty multidisciplinary network.

J Med Genet . 2020 Dec;57(12):829-834. https://doi.org/10.1136/jmedgenet-2019-106759.

Through CanVIG-UK, we have established national consensus around variant interpretation for cancer susceptibility genes via monthly national teleconferenced MDMs and collaborative data sharing using a secure online portal.

Hyder Z, Harkness EF, Woodward ER, Bowers NL, Pereira M, Wallace AJ, **Howell SJ**, **Howell A**, Lalloo F, Newman WG, Smith MJ, **Evans DG**. Risk of Contralateral Breast Cancer in Women with and without Pathogenic Variants in BRCA1, BRCA2, and TP53 Genes in Women with Very Early-Onset (<36 Years) Breast Cancer.

Cancers (Basel) 2020 Feb 7;12(2):378. https://doi.org/10.3390/cancers12020378.

Contralateral breast cancer rates are substantial in TP53, BRCA1, and BRCA2 PV carriers diagnosed with breast cancer aged 35 and under. Women need to be advised to help make informed decisions on contralateral mastectomy, guided by life expectancy from their index tumor.

Smith MJ, Woodward ER, Burghel GJ, Banks C, Morgan RD, Wallace AJ, Turnbull C, **Evans DG**. Rapid reversal of clinical down-classification of a BRCA1 splicing variant avoiding psychological harm.

Clin Genet. 2019;95(4):532-533 Dec 26. https://doi.org/10.1111/cge.13488.

It is important to obtain sufficient evidence before classifying a variant as pathogenic. This cannot rely on a single report with insufficient evidence of the proportion of abnormal splicing. Second, data from multiple sources provide greater robustness in variant classification.

Yang X, Leslie G, Doroszuk A,...**Evans DG**,... Antoniou AC, Tischkowitz M.(Multi-author) Cancer Risks Associated with Germline PALB2 Pathogenic Variants: An International Study of 524 Families.

J Clin Oncol 2020 Mar 1;38(7):674-685. https://doi.org/10.1200/JCO.19.01907.

These results confirm PALB2 as a major breast cancer susceptibility gene and establish substantial associations between germline PALB2 PVs and ovarian, pancreatic, and male breast cancers.

Bancroft EK, Saya S, Brown E, **Evans DG**, Eeles RA, Walker LG. Psychosocial effects of whole-body MRI screening in adult high-risk pathogenic TP53 mutation carriers: a case-controlled study (SIGNIFY).

J Med Genet . 2020 Apr;57(4):226-236. https://doi.org/10.1136/jmedgenet-2019-106407.

Whole Body - MRI screening can be implemented in TP53 pv carriers without adverse psychosocial outcomes in the short and medium terms.

Figlioli G, Bogliolo M, ...**Evans DG**, **Howell A** ....Manoochehri M, Manoukian S.Multi-author The FANCM : p.Arg658 * truncating variant is associated with the risk of triple-negative breast cancer.

NPJ Breast Cancer 019 Nov 1;5:38. https://doi.org/10.1038/s41523-019-0127-5.

The effect of truncating variants on breast cancer risk may depend on their position in the gene. Cell sensitivity to olaparib exposure, identifies a possible therapeutic option to treat FANCM-associated tumours.

Sun L, Brentnall A, ..., **Evans DGR**, Eccles D, Hopper J, ... Manchanda R. A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer.

JAMA Oncol. 2019 Oct 3;5(12):1718-30. https://doi.org/10.1001/jamaoncol.2019.3323.

This study found unselected, high-risk multigene testing for all patients with BC to be extremely cost-effective compared with testing based on FH or clinical criteria for UK and US health systems. These findings support changing current policy to expand genetic testing to all women with BC.

Evans DGR, Kallionpää RA, Clementi M, Trevisson E, Mautner VF, **Howell SJ**, Lewis L, Zehou O, Peltonen S, Brunello A, Harkness EF, Wolkenstein P, Peltonen J.

Breast cancer in neurofibromatosis 1: survival and risk of contralateral breast cancer in a five country cohort study.

Genet Med. 2020 Feb;22(2):398-406. https://doi.org/10.1038/s41436-019-0651-6.

Women with NF1 have a substantial contralateral breast cancer incidence and poor survival. Early start of breast cancer screening may be a way to improve the survival.

Dörk T, Peterlongo P, ... **Evans DG**, **Howell A**... Devilee P, Easton DF. (Multi-author). Two truncating variants in FANCC and breast cancer risk.

Sci Rep. 2019 Aug 29;9(1):12524. https://doi.org/10.1038/s41598-019-48804-y.

The breast cancer risk association of these two FANCC variants, if any, is much smaller than for BRCA1, BRCA2 or PALB2 mutations.

Parsons MT, Tudini E,.... **Evans DG** ...., Goldgar DE, Spurdle AB. (Multi-author)

Large scale multifactorial likelihood quantitative analysis of BRCA1 and BRCA2 variants: An ENIGMA resource to support clinical variant classification.

Hum Mutat . 2019 Sep;40(9):1557-1578. https://doi.org/10.1002/humu.23818.

We have used the multifactorial likelihood analysis approach to generate 248 new or considerably altered BRCA1/2 variant classifications, information that is relevant for medical management – including determining patient eligibility for screening or PARPi treatment, and cascade testing of their relatives.

Packwood K, Martland G,... **Evans DG**,... Birch JM, Alsalmi OA, Eccles DM. Breast cancer in patients with germline TP53 pathogenic variants have typical tumour characteristics - the Cohort study of TP53 carrier early onset breast cancer (COPE study).

J Pathol Clin Res . 2019 Jul;5(3):189-198. https://doi.org/10.1002/cjp2.133.

Aggressive HER2 positive breast cancers with densely sclerotic stroma are common in germline TP53 carriers. High levels of αvβ6 integrin, α-SMA and pSMAD2/3 expression suggest that the dense stromal phenotype may be driven by upregulated transforming growth factor beta signalling.

Evans DG, **Howell SJ**, Peltonen J. Association Between Invasive Lobular Breast Cancer and Mutations in the Mismatch Repair Gene MSH6.

JAMA Oncol. 2019 Jan 1;5(1):119-120. https://doi.org/10.1001/jamaoncol.2018.6905.

Comment

Grimmett C, Brooks C, Recio-Saucedo A, **Armstrong A**, Cutress RI, **Evans DG**, et al Development of Breast Cancer Choices: a decision support tool for young women with breast cancer deciding whether to have genetic testing for BRCA1/2 mutations.

Support Care Cancer. 2019 Jan;27(1):297-309. https://doi.org/10.1007/s00520-018-4307-x.

This decision support tool had considerable clinical utility as an adjunct to genetic counselling or for use in busy oncology clinics where formal genetic counselling may be unavailable.

2.3 Risk adapted screening

McWilliams L, Woof VG, Donnelly LS, **Howell A**, **Evans DG**, French DP Risk stratified breast cancer screening: UK healthcare policy decision-making stakeholders' views on a low-risk breast screening pathway.

BMC Cancer. 2020 Jul 22;20(1):680. https://doi.org/10.1186/s12885-020-07158-9.

National healthcare policy decision-makers appear to believe that risk-stratified breast screening is acceptable, in principle. It will however be essential to address key obstacles prior to implementation in national programmes.

French DP, **Astley S**, ..**Harvie M**, **Howell A**, ...**Maxwell AJ**, McWilliams L,... , **Evans DG**. What are the benefits and harms of risk stratified screening as part of the NHS breast screening Programme? Study protocol for a multi-site non-randomised comparison of BC-predict versus usual screening (NCT04359420).

BMC Cancer. 2020 Jun 18;20(1):570. https://doi.org/10.1186/s12885.

We will assess the feasibility of integrating BC-Predict into the NHSBSP and identify the main uncertainties for a definitive evaluation of the clinical and cost-effectiveness of BC-Predict.

Brentnall AR, ...,**Astley SM**,... **Howell A**, Newman WG, Cuzick J, **Evans DGR**. A case-control evaluation of 143 single nucleotide polymorphisms for breast cancer risk stratification with classical factors and mammographic density.

Int J Cancer. 2020 Apr 15;146(8):2122-2129. https://doi.org/10.1002/ijc.32541.

Polygenic risk scores based on many SNPs improve risk stratification in combination with classical risk factors and mammographic density, and SNP143 was similarly predictive for ER-positive and ER-negative disease.

Evans DGR, Harkness EF, ..**Howell SJ**, **Maxwell AJ**, **Howell A**,... Newman WG, Cuzick J. Breast cancer pathology and stage are better predicted by risk stratification models that include mammographic density and common genetic variants.

Breast Cancer Res Tr. 2019 Jul;176(1):141-148. https://doi.org/10.1007/s10549-019-05210-2.

A combined approach using the Tyrer-Cuzick model with mammographic density and a polygenic risk score provides accurate risk stratification, particularly for poor prognosis cancers. This provides support for reducing the screening interval in high-risk women and increasing the screening interval in low-risk women defined by this model.

Rainey L, van der Waal D, Jervaeus A, Donnelly LS, **Evans DG**, Hammarström M, Hall P, Wengström Y, Broeders MJM. European women's perceptions of the implementation and organisation of risk-based breast cancer screening and prevention: a qualitative study.

BMC Cancer. 2020 Mar 24;20(1):247. https://doi.org/10.1016/j.breast.2018.02.029.

Women eligible for breast cancer screening in the Netherlands, the United Kingdom, and Sweden participated in focus group discussions on the mechanism of potential introduction of risk adapted screening. Women's insights identified the need for country-specific standardised protocols regarding the assessment and communication of risk, and the provision of heterogeneous screening and prevention recommendations.

Rainey L, Jervaeus A, Donnelly LS, **Evans DG**, Hammarström M, Hall P, Wengström Y, Broeders MJM, van der Waal D. Women's perceptions of personalised risk-based breast cancer screening and prevention: an international focus group study.

Psychooncology. 2019 May;28(5):1056-1062. https://doi.org/10.1002/pon.5051.

Women's insights identified the need for country-specific standardised protocols regarding the assessment and communication of risk, and the provision of heterogeneous screening and prevention recommendations, monitoring the principle of solidarity in healthcare policy.

2.4 Screening

Squires S, Ionescu G, ...Evans DG, Maxwell A, Howell S, Astley SM. Automatic density prediction in low dose mammography.

In 15th International Workshop on Breast Imaging (IWBI2020) 2020 May 22 (Vol. 11513, p. 115131D). https://doi.org/10.1117/12.2564714. International Society for Optics and Photonics.

Woof VG, Ruane H, French DP, Ulph F, Qureshi N, Khan N, Evans DG, Donnelly LS. The introduction of risk stratified screening into the NHS breast screening Programme: views from British-Pakistani women.

BMC Cancer. 2020 May 20;20(1):452. https://doi.org/10.1186/s12885-020-06959-2.

The idea of risk stratification was favourable amongst this underserved community. To avoid exacerbating inequities, this new service should provide information in multiple languages and modalities and offer women the opportunity to speak to a healthcare professional about risk.

Du-Crow E, Astley SM, Hulleman J. Suspicious minds: effect of using a lesion likelihood score on reader behaviour with interactive mammographic CAD.

In 15th International Workshop on Breast Imaging (IWBI2020) 2020 May 22 (Vol. 11513, p. 115130Y). https://doi.org/10.1117/12.2556472. International Society for Optics and Photonics.

Aloufi AS, ...Harkness EF, Astley S. Breast density in Saudi Arabia: intra and inter reader variability in screening mammograms assessed visually using BI-RADS and visual analogue scales.

In: Medical Imaging 2020: Image Perception, Observer Performance, and Technology Assessment 2020 Mar 16 (Vol. 11316, p. 113160H). https://doi.org/10.1117/12.2548758. International Society for Optics and Photonics.

Du-Crow E, Astley SM, Hulleman J. Is there a safety-net effect with computer-aided detection?

J Med Imaging (Bellingham) 2020 Mar;7(2):022405. https://doi.org/10.1117/1.JMI.7.2.022405.

These results suggest that the initial search may be influenced by the subsequent availability of CAD; if so, cross-sectional CAD efficacy studies should account for the effect when estimating benefit.

Woof VG, Ruane H, Ulph F, French DP, Qureshi N, Khan N, Evans DG, Donnelly LS. Engagement barriers and service inequities in the NHS Breast Screening Programme: Views from British-Pakistani women.

J Med Screen. 2019 Dec 2:969141319887405.

British-Pakistani women face some unique challenges when accessing breast screening. To promote uptake, the service needs to address the translation of screening materials and optimize upon community networks to disseminate knowledge, including knowledge of the screening environment within the context of culture to promote informed choice about attendance.

Evans DG, Edwards M, Duffy SW; Cancer Genetics Group clinical leads, Tischkowitz M. Sporadic implementation of UK familial mammographic surveillance guidelines 15 years after original publication.

Br J Cancer. 2020 Feb;122(3):329-332. https://doi.org/10.1038/s41416-019-0631-2.

There is major inequity in provision for screening and a postcode lottery exists for the management of women from families with a history of breast cancer. We estimate that up to 73 preventable breast cancer deaths occur each year due to the current inequity of access.

Long H, Brooks JM, Harvie M, Maxwell A, French DP. How do women experience a false-positive test result from breast screening? A systematic review and thematic synthesis of qualitative studies.

Br J Cancer. 2019 Aug;121(4):351-358. https://doi.org/10.1038/s41416-019-0524-4.

The way healthcare professionals verbally communicate results to women may contribute to lasting breast cancer-related worry. Women need more reassurance, emotional support and answers to their questions before and during screening assessment, and after receiving their result.

Ionescu GV, Fergie M, Brentnall AR, Cuzick J, Evans DG, Astley SM. Prediction of reader estimates of mammographic density using convolutional neural networks.

J Med Imaging (Bellingham) 2019 Jul;6(3):031405. https://doi.org/10.1117/1.JMI.6.3.031405.

Our fully automated method shows promising results for cancer risk prediction and is comparable with human performance.

Evans DG, Thomas S, ..., Howell A, Wilson M, Fox R,.... Duffy S, FH02 study group. Final Results of the Prospective FH02 Mammographic Surveillance Study of Women Aged 35–39 at Increased Familial Risk of Breast Cancer.

EClinicalMedicine 2019; Jan;7:39-46. https://doi.org/10.1016/j.eclinm.2019.01.005.

Mammography screening aged 35-39 years detects breast cancer at an early stage and is likely to be as effective in reducing mortality as in women at increased breast cancer risk aged 40-49 years.

2.5 Lifestyle

Hewitt RM, Pegington M, Harvie M, French DP. How acceptable is a weight maintenance programme for healthy weight young women who are at increased risk of breast cancer?

Psychol Health. 2020 Jul;35(7):854-871. https://doi.org/10.1080/08870446.2019.1690146.

A weight gain prevention intervention that focuses on wellbeing and behaviour change appears acceptable to many healthy weight women. Future research should examine whether women's expressed acceptability translates into actual acceptability of such a programme.

Pegington M, French DP, Harvie MN.

Why young women gain weight: A narrative review of influencing factors and possible solutions.

Obes Rev . 2020 May;21(5):e13002. https://doi.org/10.1111/obr.13002.

Weight gain is mediated by lack of knowledge and skills around food and nutrition, depression, anxiety, stress, satiety, neural responses, and possibly sleep patterns and premenstrual cravings. There is a need to address evidence gaps highlighted and implement what is currently known to develop effective strategies to limit weight gain in young women.

Renehan A, Pegington M, Harvie M, Sperrin M, Astley S, Brentnall A, Howell A, Cuzick J, Evans DG. Young adulthood body mass index, adult weight gain and breast cancer risk: the PROCAS Study (United Kingdom).

Brit J Cancer 2020 Mar 23. https://doi.org/10.1038/s41416-020-0807-9.

Adult weight gain increased post-menopausal breast cancer risk only among women who were <23.4 kg/m2 aged 20 years.

Harvie M, Pegington M, French D, Cooper G, McDiarmid S, Howell A, Donnelly L, Ruane H, Sellers K, Foden P, Evans DG. Breast cancer risk status influences uptake, retention and efficacy of a weight loss programme amongst breast cancer screening attendees: two randomised controlled feasibility trials.

BMC Cancer. 2019 Dec 4;19(1):1089. https://doi.org/10.1186/s12885-019-6279-8.

Women who are informed that they are at increased breast cancer risk were significantly more likely to join and remain in the programmes and consequently lose more weight across both studies. High risk women are more likely engage in a lifestyle prevention programme and have the greatest potential benefit from risk reduction strategies.

Li H, Terry MB, Antoniou AC, Phillips KA, ..., Evans DG,.... Goldgar DE.(Multiauthor) Alcohol consumption, cigarette smoking, and risk of breast cancer for BRCA1 and BRCA2 mutation carriers: results from The BRCA1 and BRCA2 Cohort Consortium.

Cancer Epidemiol Biomarkers Prev. 2019 Dec 2. pii: cebp.0546.2019. https://doi.org/10.1158/1055-9965.EPI-19-0546.

The finding that smoking during the pre-reproductive years increases breast cancer risk for mutation carriers warrants further investigation.

Pegington M, Evans DG, Howell A, Donnelly LS, Wiseman J, Cuzick JM, Harvie MN. Lifestyle behaviours and health measures of women at increased risk of breast cancer taking chemoprevention.

Eur J Cancer Prev. 2019 Nov;28(6):500-506. https://doi.org/10.1097/CEJ.0000000000000493.

Women taking chemoprevention had a high prevalence of unhealthy lifestyle behaviours and health measures, like an age-matched English cohort. Improving these measures in women at increased BC risk could significantly decrease rates of BC and other noncommunicable diseases.

Harvie M, Pegington M, McMullan D, Morris J, Howell S, Howell A. The effectiveness of home versus community-based weight control programmes initiated soon after breast cancer diagnosis: a randomised controlled trial.

Br J Cancer. 2019 Sep;121(6):443-454. https://doi.org/10.1038/s41416-019-0522-6.

The programmes were equally effective for weight control, but the community programme had additional benefits.

Panizza CE, Lim U, Yonemori KM, Cassel KD, Wilkens LR, **Harvie MN**. Effects of Intermittent Energy Restriction Combined with a Mediterranean Diet on Reducing Visceral Adiposity: A Randomized Active Comparator Pilot Study.

Nutrients 2019 Jun 20;11(6):1386. https://doi.org/10.3390/nu11061386.

Results demonstrate IER+MED is acceptable, lowers visceral and total adiposity among East Asian Americans, and may improve liver function more effectively than a healthful diet pattern.

Shu X, Wu L, Khankari NK, Shu XO, ...**Evans DG**. **Howell A**... Easton DF, Zheng W; Breast Cancer Association Consortium (Multi-author). Associations of obesity and circulating insulin and glucose with breast cancer risk: a Mendelian randomization analysis.

Int J Epidemiol. 2019 Jun 1;48(3):795-806. https://doi.org/10.1093/ije/dyy201.

The previously reported inverse association of genetically predicted BMI with breast cancer risk, and showed a positive association of genetically predicted fasting insulin and 2-h glucose and an inverse association of WHRadj BMI with breast cancer risk was confirmed. Our study suggests that genetically determined obesity and glucose/insulin-related traits have an important role in the aetiology of breast cancer.

Ooi BNS, Loh H, Ho PJ, ... **Evans DG**, ...Easton D, Hartman M, Li J. (Multi-author). The genetic interplay between body mass index, breast size and breast cancer risk: a Mendelian randomization analysis.

Int J Epidemiol . 2019 Jun 1;48(3):781-794. https://doi.org/10.1093/ije/dyz124.

Our findings indicate a potential positive causal association between BMI and breast size and a potential negative causal association between BMI and breast cancer risk. We found no clear evidence for a direct relationship between breast size and breast cancer risk.

Renehan AG, Martin RM, **Evans DG**. Cancer surveillance, obesity, and potential bias.

Lancet Public Health. 2019 May;4(5):e218 https://doi.org/10.1016/S2468-2667(19)30058-1.

We champion triangulation (the combination of evidence from studies that yield causal estimates with different potential sources of bias, but where these biases are independent), and inclusion of the use of non-conventional approaches, such as instrumental variable analyses.

Qian F, Wang S, Mitchell J, **Evans DG** ....Rebbeck TR, Huo D. (Multi-author) Height and Body Mass Index as Modifiers of Breast Cancer Risk in BRCA1/2 Mutation Carriers: A Mendelian Randomization Study.

J Natl Cancer Inst. 2019 Apr 1;111(4):350-364. https://doi.org/10.1093/jnci/djy132.

Height is associated with overall breast cancer and BMI is associated with premenopausal breast cancer in BRCA1/2 mutation carriers. Incorporating height and BMI, particularly genetic score, into risk assessment may improve cancer management.

Kar SP, Andrulis IL,... , **Evans DGR**, ...Wendt C, Zheng W, Pharoah PDP (Multi-author).

The association between weight at birth and breast cancer risk revisited using Mendelian randomisation.

Eur J Epidemiol. 2019 Feb 8. https://doi.org/10.1007/s10654-019-00485-7.

Point estimates of the odds ratios from most analyses performed indicated an inverse relationship between genetically predicted BW and breast cancer, but we are unable to rule out an association between the non-genetically determined component of BW and breast cancer. Thus, genetically predicted higher BW was not associated with an increased risk of breast cancer in adult life in our MR study.

Gandhi A, Copson E, ...**Howell A**, Morris J, **Howell S**,... **Gareth Evans D**, **Harvie M**.

Predictors of weight gain in a cohort of premenopausal early breast cancer patients receiving chemotherapy.

Breast. 2019 Feb 15;45:1-6. https://doi.org/10.1016/j.breast.2019.02.006.

Almost a third of premenopausal patients receiving adjuvant chemotherapy for breast cancer will gain clinically significant weight and over 40% will have central obesity 12-months following diagnosis. A greater weight gain is predicted by lower pretreatment BMI.

2.6 Chemoprevention

Hale MJ, **Howell A**, Dowsett M, Cuzick J, Sestak I.

Tamoxifen related side effects and their impact on breast cancer incidence: A retrospective analysis of the randomised IBIS-I trial.

Breast. 2020 Oct 31;54:216-221. https://doi.org/10.1016/j.breast.2020.10.015.

Overall, no association between side effects reported at 6 months and subsequent breast cancer occurrence was observed. Some side effects might be useful markers for breast cancer occurrence in postmenopausal women.

Brentnall AR, Warren R, Harkness EF, **Astley SM**, Wiseman J, Fox J, Fox L, Eriksson M, Hall P, Cuzick J, **Evans DG**, **Howell A**. Mammographic density change in a cohort of premenopausal women receiving tamoxifen for breast cancer prevention over 5 years.

Breast Cancer Res. 2020 Sep 29;22(1):101. https://doi.org/10.1186/s13058-020-01340-4.

All measures showed a consistent and large average tamoxifen-induced change in density over the first year, and a continued decline thereafter. However, these measures of density change at 1 year were not stable on an individual basis.

Cuzick J, Sestak I, Forbes JF, Dowsett M, Cawthorn S, Mansel RE, Loibl S, Bonanni B, **Evans DG**, **Howell A**; IBIS-II investigators Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial.

Lancet. 2020 Jan 11;395(10218):117-122. https://doi.org/10.1016/S0140-6736(19)32955-1.

This analysis has identified a significant continuing reduction in breast cancer with anastrozole in the post-treatment follow-up period, with no evidence of new late side-effects. Further follow-up is needed to assess the effect on breast cancer mortality.

3.0 Surgical studies

3.1 Surgery related trials

Smith I, Robertson J, Kilburn L, Wilcox M, Evans A, Holcombe C, Horgan K, **Kirwan C**, Mallon E, Sibbering M, Skene A, Vidya R, Cheang M, Banerji J, Morden J, Sidhu K, Dodson A, Bliss JM, Dowsett M. Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial.

Lancet Oncol. 2020 Nov;21(11):1443-1454. https://doi.org/10.1016/S1470-2045(20)30458-7.

Perioperative aromatase inhibitor therapy (POAI) has not been shown to improve treatment outcome but can be used without detriment to help select appropriate adjuvant therapy based on tumour Ki67. Most patients with low Ki67 or low POAI-induced Ki67 do well with adjuvant standard endocrine therapy (considering clinical-pathological factors), whereas those whose POAI-induced Ki67 remains high might benefit from further adjuvant treatment or trials of new therapies.

Castle J, Blower E, **Bundred NJ**, Harvey JR, Thachil J, Marshall A, Cox K, Cicconi S, Holcombe C, Palmieri C, **Kirwan CC**. Rivaroxaban compared to no treatment in ER-negative stage I-III early breast cancer patients (the TIP Trial): study protocol for a phase II preoperative window-of-opportunity study design randomised controlled trial.

Trials. 2020 Aug 27;21(1):749. https://doi.org/10.1186/s13063-020-04675-7.

Preoperative randomised study to test the effect of the anticoagulant, Rivaroxoban on in tumour Ki67, apoptosis and angiogenesis as a prelude to potential use to prevent breast cancer recurrence.

Robertson JF, Evans A, Henschen S, **Kirwan CC**, Jahan A, Kenny LM, Dixon JM, Schmid P, Kothari A, Mohamed O, Fasching PA, Cheung KL, Wuerstlein R, Carroll D, Klinowska T, Lindemann JPO, MacDonald A, Mather R, Maudsley R, Moschetta M, Nikolaou M, Roudier MP, Sarvotham T, Schiavon G, Zhou D, Zhou L, Harbeck N. A randomized, window of opportunity study comparing the effects of the novel oral SERD AZD9496 with fulvestrant in patients with ER+ HER2- primary breast cancer.

Clin Cancer Res 2020 Aug 15;26(16):4242-4249. https://doi.org/10.1158/1078-0432.CCR-19-3387.

This was the first presurgical study to demonstrate that an oral selective estrogen receptor downreulator (SERD) affects its key biological targets. However, the oral SERD, AZD9496 was not superior to the intramuscular SERD, fulvestrant, at the dose tested.

Courtney A, O'Connell R, Rattay T, Kim B, Cutress RI, **Kirwan CC**, **Gandhi A**, Fairbrother P, Sharma N, Cartlidge CWJ, Horgan K, McIntosh SA, Leff DR, Vidya R, Potter S, Holcombe C, Copson E, Coles CE, **Dave RV**. The B-MaP-C study: Breast cancer management pathways during the COVID-19 pandemic. Study protocol.

Int J Surg Protoc. 2020;24:1-5. https://doi.org/10.1016/j.isjp.2020.07.003.

The primary aim of the B-MaP-C study is to audit and describe breast cancer management of patients newly diagnosed with breast cancer during the COVID-19 pandemic against pre-COVID-19 management practice in the UK.

Murray Brunt A, Haviland JS, Wheatley DA, Sydenham MA, Alhasso A, Bloomfield DJ, Chan C, Churn M, Cleator S, Coles CE, Goodman A, Harnett A, Hopwood P, Kirby AM, **Kirwan CC**, Morris C, Nabi Z, Sawyer E, Somaiah N, Stones L, Syndikus I, Bliss JM, Yarnold JR; FAST-Forward Trial Management Group. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial.

Lancet. 2020 May 23;395(10237):1613-1626. https://doi.org/10.1016/S0140-6736(20)30932-6.

26 Gy in five fractions over 1 week is non-inferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumour control and is as safe in terms of normal tissue effects up to 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer.

Irwin GW, Bannon F, Coles CE, Copson E, Cutress RI, **Dave RV**, Grayson M, Holcombe C, Irshad S, **O'Brien C**, O'Connell RL, Palmieri C, Shaaban AM, Sharma N, Singh J, Whitehead I, Potter S, McIntosh SA. The NeST (neoadjuvant systemic therapy in breast cancer) study - Protocol for a prospective multi-centre cohort study to assess the current utilization and short-term outcomes of neoadjuvant systemic therapies in breast cancer.

Int J Surg Protoc. 2019 Nov 11;18:5-11. https://doi.org/10.1016/j.isjp.2019.10.002.

Protocol

Bhattacharya IS, Haviland JS, Perotti C, Eaton D, Gulliford S, Harris E, Coles CE, **Kirwan CC**, Bliss JM, Kirby AM; IMPORT Trialists. Is breast seroma after tumour resection associated with patient-reported breast appearance change following radiotherapy? Results from the IMPORT HIGH (CRUK/06/003) trial.

Radiother Oncol. 2019 Jul;136:190-196. https://doi.org/10.1016/j.radonc.2019.03.022.

Seroma was not associated with patient-reported breast appearance change, but haematoma and smoking were significant risk factors.

Bhattacharya IS, Haviland JS, Kirby AM, **Kirwan CC**, Hopwood P, Yarnold JR, Bliss JM, Coles CE; IMPORT Trialists. Patient-Reported Outcomes Over 5 Years After Whole- or Partial-Breast Radiotherapy: Longitudinal Analysis of the IMPORT LOW (CRUK/06/003) Phase III Randomized Controlled Trial.

J Clin Oncol. 2019 Feb 1;37(4):305-317. https://doi.org/10.1200/JCO.18.00982.

IMPORT LOW demonstrated noninferiority of partial-breast and reduced-dose radiotherapy versus whole-breast radiotherapy for local relapse and similar or reduced toxicity at 5 years. Analysis by treatment group showed average number of adverse events s per person was lower in partial-breast and reduced-dose versus whole-breast group and decreased over time in all groups.

3.2 Breast reconstruction

Dave RV, Vucicevic A, Highton L, **Harvey JR**, Johnson R, **Kirwan CC**, Murphy J. Medium term outcomes following immediate prepectoral implant-based breast reconstruction using acellular dermal matrix

Br J Surg . 2020 Sep 29. https://doi.org/10.1002/bjs.11964.

A total of 469 reconstructions were undertaken in 289 women. Minor complications were seen after 11·2% of reconstructions, major complications after 5·9%, and the rate of implant loss by 3 months was 3·1%. Prepectoral implant-based breast reconstruction has acceptable medium-term results but careful patient selection is advised.

Harvey KL, Mills N, White P, Holcombe C, Potter S; Pre-BRA Feasibility Study Steering Group.

Pre-BRA Feasibility Study Steering Group: (**Cliona Kirwan**) The Pre-BRA (pre-pectoral Breast Reconstruction EvAluation) feasibility study: protocol for a mixed-methods IDEAL 2a/2b prospective cohort study to determine the safety and effectiveness of prepectoral implant-based breast reconstruction.

BMJ Open. 2020 Jan 26;10(1):e033641 https://doi.org/10.1136/bmjopen-2019-033641.

Protocol

Potter S, Trickey A, Rattay T, O'Connell RL, **Dave R**, Baker E, Whisker L, Skillman J, Gardiner MD, Macmillan RD, Holcombe C; TeaM and iBRA-2 Steering Groups, the Breast Reconstruction Research Collaborative, and the Mammary Fold Academic and Research Collaborative, Therapeutic mammaplasty is a safe and effective alternative to mastectomy with or without immediate breast reconstruction.

Br J Surg. 2020 Jun;107(7):832-844. https://doi.org/10.1002/bjs.11468.

A therapeutic mammoplasty (TM) is a surgical procedure to remove breast cancer and reshape the breast by removing tissue and skin. Breast conservation was possible in 87% of patients who had TM, and TM did not delay adjuvant treatment.

Fakim B, Highton L, **Gandhi A**, Johnson R, Murphy J. Implant-based breast reconstruction with Artia™ tissue matrix.

J Plast Reconstr Aesthet Surg. 2019 Sep;72(9):1548-1554 https://doi.org/10.1016/j.bjps.2019.05.024.

Artia™ (LifeCell, NJ), a new porcine acellular dermal matrix (ADM). This is one of the first studies demonstrating that Artia™-assisted implant-based breast reconstruction is associated with low and acceptable early complication rates. The results show an implant loss rate of 4.9% across 500 ADM-assisted implant reconstructions.

Rachel L O'Connell, Tim Rattay, **Rajiv V Dave**, Adam Trickey, Joanna Skillman, Nicola L P Barnes, Matthew Gardiner, Adrian Harnett, Shelley Potter, Chris Holcombe, iBRA-2 Steering Group; Breast Reconstruction Research Collaborative. The Impact of Immediate Breast Reconstruction on the Time to Delivery of Adjuvant Therapy: The iBRA-2 Study

Br J Cancer. 2019 Apr;120(9):883-895. https://doi.org/10.1038/s41416-019-0438-1.

Immediate breast reconstruction does not result in clinically significant delays to adjuvant therapy, but post-operative complications are associated with treatment delays.

3.3 Diagnosis and reduction of recurrence

Bundred J, Michael S, Bowers S, Barnes N, Jauhari Y, Plant D, Maishman T, Cutress R, Holleczek B, Dodwell D, **Bundred N**. Do surgical margins matter after mastectomy? A systematic review.

Eur J Surg Oncol. 2020 Dec;46(12):2185-2194. https://doi.org/10.1016/j.ejso.2020.08.015.

Failure to achieve clear margins after mastectomy may increase the risks of local and distant recurrence. Adequate margin clearance should be recommended to minimize recurrence after mastectomy in National and International Guidelines.

Bundred NJ, Dodwell D, Bundred JR, Cutress RI. Residual disease after mastectomy.

Lancet Oncol. 2020 Nov;21(11):e499. https://doi.org/10.1016/S1470-2045(20)30542-8.

Comment

Bundred N, Foden P, Todd C, Morris J, Watterson D, Purushotham A, Bramley M, Riches K, Hodgkiss T, Evans A, Skene A, Keeley V; Investigators of BEA/PLACE studies. Increases in arm volume predict lymphoedema and quality of life deficits after axillary surgery: a prospective cohort study.

Br J Cancer. 2020 Jul;123(1):17-25. https://doi.org/10.1038/s41416-020-0844-4.

Relative arm volume increase measurement was the best diagnostic tool for lymphoedema. Bioimpedance spectroscopy alone is not appropriate for lymphoedema screening or diagnosis. BMI > 30 predicted lymphoedema diagnosis and progression.

Zacharioudakis K, Down S, Bholah Z, Lee S, Khan T, **Maxwell AJ**, Howe M, **Harvey J**.

Is the future magnetic? Magseed localisation for non palpable breast cancer. A multi-centre non randomised control study.

Eur J Surg Oncol. 2019 Nov;45(11):2016-2021. https://doi.org/10.1016/j.ejso.2019.06.035.

Magseed is an alternative method of localising non-palpable breast lesions and consists of a paramagnetic seed that can be visualised on mammography and ultrasound. In our series Magseed localisation proved to be as reliable and effective as WGL in terms of lesion identification, excision with tumour free margins and specimen weight.

Somasundaram SK, Potter S, Elgammal S, **Maxwell AJ**, Sami AS, Down SK, **Dave RV, Harvey J**.

Impalpable breast lesion localisation, a logistical challenge: results of the UK iBRA-NET national practice questionnaire.

Breast Cancer Res Treat 2020 Sep 10. https://doi.org/10.1007/s10549-020-05918-6.

Wires are currently the most used localisation technique but are associated with significant logistical issues. Newer techniques (eg Magseed) may offer a better solution but will need robust evaluation before they are adopted to ensure safety and efficacy.

Gandhi A, Coles C, Makris A, Provenzano E, Goyal A, **Maxwell AJ**, Doughty J.

Axillary Surgery Following Neoadjuvant Chemotherapy - Multidisciplinary Guidance from the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology and British Society of Breast Radiology.

Clin Oncol (R Coll Radiol). 2019 Sep;31(9):664-668. https://doi.org/10.1016/j.clon.2019.05.021.

Guidance

Bundred N, Todd C, Morris J, Keeley V, Purushotham A, Bagust A, Foden P, Bramley M, Riches K. Individualising breast cancer treatment to improve survival and minimise complications in older women: a research programme including the PLACE RCT.

Southampton (UK): NIHR Journals Library; 2019 Aug. PMID: 31436943.

Lymphoedema reduces QoL and changes in arm volume of > 9% predicted lymphoedema requiring and benefiting from sleeve application.

Boundouki G, Wong JR, Hee S, Croghan N, Stocking K, Pieri A, Critchley A, **Kirwan CC**, **Harvey JR**. Comparing Long-Term Local Recurrence Rates of Surgical and Non-Surgical Management of Close Anterior Margins in Breast Conserving Surgery

Breast Cancer Res Treat 2019 Jul;176(2):311-319. https://doi.org/10.1007/s10549-019-05242-8.

There are few data on the management of cancer involved anterior compared with lateral margins of a tumour. This study shows that non-surgical management (non-resection) of close anterior margins appears oncologically safe when combined with appropriate adjuvant therapy.

3.4 Surgery and COVID 19

Courtney A, O'Connell R, Rattay T, Kim B, Cutress RI, **Kirwan CC**, **Gandhi A**, Fairbrother P, Sharma N, Cartlidge CWJ, Horgan K, McIntosh SA, Leff DR, Vidya R, Potter S, Holcombe C, Copson E, Coles CE, **Dave RV**. The B-MaP-C study: Breast cancer management pathways during the COVID-19 pandemic. Study protocol.

Int J Surg Protoc. 2020;24:1-5. https://doi.org/10.1016/j.isjp.2020.07.003.

Protocol

Highton LR, **Dave RV**, Barnes NLP.

Breast cancer surgery during the COVID-19 pandemic.

Br J Surg. 2020 Jul 20:10.1002/bjs.11819. https://doi.org/10.1002/bjs.11819.

The partnership between the NHS and private hospitals, along with strong leadership, teamwork and careful planning have allowed us to continue to offer safe breast surgery during the pandemic. Measures including pre-operative SARS-CoV-2 throat swabs, a change in surgical practice and virtual follow-up have helped to safeguard patients and staff.

4.0 Systemic therapy

4.1 HER2 based therapy

Verrill M, **Wardley AM**, Retzler J, Smith AB, Bottomley C, Ní Dhochartaigh S, Tran I, Leslie I, Schmid P. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage.

Health Qual Life Outcomes. 2020 Nov 2;18(1):353. https://doi.org/10.1186/s12955-020-01603-w.

Metastatic disease and treatment of HER2-positive BC adversely impacted on work productivity and health related quality of life. The results of this study support the idea that being able to delay or prevent the metastatic recurrence of BC, for example by extending the time patients are in remission or at early stage of BC, has wider benefits in terms of patient productivity and health related quality of life.

Earl H, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L, Rea D, Howe D, Raynes K, Higgins HB, Wilcox M, Plummer C, Mahler-Araujo B, Provenzano E, Chhabra A, Gasson S, Balmer C, Abraham JE, Caldas C, Hall P, Shinkins B, McCabe C, Hulme C, Miles D, **Wardley AM**, Cameron DA, Dunn JA. Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT.

Health Technol Assess. 2020 Aug;24(40):1-190. https://doi.org/10.3310/hta24400.

PERSEPHONE demonstrated that, in the treatment of HER2-positive early breast cancer, 6 months' adjuvant trastuzumab is non-inferior to 12 months'. Six months' treatment resulted in significantly less cardiac toxicity and fewer severe adverse events.

Howell SJ, Coe F, Wang X, Horsley L, Ekholm M. Carboplatin dose capping affects pCR rate in HER2-positive breast cancer patients treated with neoadjuvant Docetaxel, Carboplatin, Trastuzumab, Pertuzumab (TCHP).

Breast Cancer Res Treat. 2020 Aug 29. https://doi.org/10.1007/s10549-020-05868-z.

The overall pCR rate was high in patients with HER2+ breast cancer receiving the TCHP regimen; however, carboplatin dose capping resulted in inferior pCR rates, particularly in the ER+ subgroup.

Tolaney SM, **Wardley AM**, Zambelli S, Hilton JF, Troso-Sandoval TA, Ricci F, Im SA, Kim SB, Johnston SR, Chan A, Goel S, Catron K, Chapman SC, Price GL, Yang Z, Gainford MC, André F. Abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus standard-of-care chemotherapy in women with hormone receptor-positive, HER2-positive advanced breast cancer (monarcHER): a randomised, open-label, phase 2 trial.

Lancet Oncol. 2020 Jun;21(6):763-775. https://doi.org/10.1016/S1470-2045(20)30112-1.

The monarcHER trial aimed to compare the efficacy of abemaciclib plus trastuzumab with or without fulvestrant with standard-of-care chemotherapy plus trastuzumab in women with advanced breast cancer. The combination of abemaciclib, fulvestrant, and trastuzumab significantly improved progression-free survival versus standard-of-care chemotherapy plus trastuzumab suggesting that a chemotherapy-free regimen might be an option for patients with hormone receptor-positive, HER2-positive advanced breast cancer.

Lin NU, Borges V, Anders C, Murthy RK, Paplomata E, Hamilton E, Hurvitz S, Loi S, Okines A, Abramson V, Bedard PL, Oliveira M, Mueller V, Zelnak A, DiGiovanna MP, Bachelot T, Chien AJ, O'Regan R, **Wardley A**, Conlin A, Cameron D, Carey L, Curigliano G, Gelmon K, Loibl S, Mayor J, McGoldrick S, An X, Winer EP. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial.

J Clin Oncol. 2020 May 29:JCO2000775. https://doi.org/10.1200/JCO.20.00775.

In patients with HER2-positive breast cancer with brain metastases, the addition of tucatinib to trastuzumab and capecitabine doubled response rate, reduced risk of intracranial progression or death by two thirds, and reduced risk of death by nearly half. This is the first regimen to demonstrate improved antitumor activity against brain metastases in patients with HER2-positive breast cancer.

Earl HM, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L, Harnett AN, Ah-See ML, Simcock R, Rea D, Raj S, Woodings P, Harries M, Howe D, Raynes K, Higgins HB, Wilcox M, Plummer C, Mansi J, Gounaris I, Mahler-Araujo B, Provenzano E, Chhabra A, Abraham JE, Caldas C, Hall PS, McCabe C, Hulme C, Miles D, **Wardley AM**, Cameron DA, Dunn JA; PERSEPHONE Steering Committee and Trial Investigators. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial.

Lancet. 2019 Jun 29;393(10191):2599-2612. https://doi.org/10.1016/S0140-6736(19)30650-6.

This study demonstrated that 6-month trastuzumab treatment is non-inferior to 12-month treatment in patients with HER2-positive early breast cancer, with less cardiotoxicity and fewer severe adverse events. These results support consideration of reduced duration trastuzumab for women at similar risk of recurrence as to those included in the trial.

Shi W, Jiang T, Nuciforo P, Hatzis C, Holmes E, Harbeck N, Sotiriou C, Peña L, Loi S, Rosa DD, Chia S, **Wardley A**, Ueno T, Rossari J, Eidtmann H, Armour A, Piccart-Gebhart M, Rimm DL, Baselga J, Pusztai L. Pathway level alterations rather than mutations in single genes predict response to HER2-targeted therapies in the neo-ALTTO trial.

Ann Oncol. 2019 Jun 1;30(6):1018. https://doi.org/10.1093/annonc/mdy530.

Mutations in the RhoA pathway are associated with pCR to lapatinib and mutations in a PIK3CA-related network are associated with resistance to trastuzumab. The combined mutation status of these two pathways could define patients with very low response rate to trastuzumab alone that can be augmented by adding lapatinib or substituting trastuzumab with lapatinib.

Bachelot T, Ciruelos E, Schneeweiss A, Puglisi F, Peretz-Yablonski T, Bondarenko I, Paluch-Shimon S, **Wardley A**, Merot JL, du Toit Y, Easton V, Lindegger N, Miles D; PERUSE investigators. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE).

Ann Oncol. 2019 May 1;30(5):766-773. https://doi.org/10.1093/annonc/mdz061.

PERUSE was designed to assess the safety and efficacy of investigator-selected taxane with pertuzumab and trastuzumab in this setting. The study demonstrated that paclitaxel was an equally effective taxane to docetaxel.

4.2 Other targeted therapy

Pascual J, Lim JSJ, Macpherson IRJ, **Armstrong AC**, Ring A, Okines AF, Cutts RJ, Herrera-Abreu MT, Garcia-Murillas I, Pearson A, Hrebien S, Gevensleben H, Proszek PZ, Hubank M, Hills M, King J, Parmar M, Prout T, Finneran L, Malia J, Swales KE, Ruddle R, Raynaud FI, Turner A, Hall E, Yap TA, Lopez JS, Turner NC. Triplet therapy with palbociclib, taselisib and fulvestrant in PIK3CA mutant breast cancer and doublet palbociclib and taselisib in pathway mutant solid cancers.

Cancer Discov. 2020 Sep 21:CD-20-0553. https://doi.org/10.1158/2159-8290.CD-20-0553.

The triplet therapy response rate in PIK3CA mutant, ER-positive HER2-negative was 37.5% (95% CI 18.8-59.4). Durable disease control was observed in PIK3CA mutant ER-negative breast cancer with doublet therapy.

Robson M, Ruddy KJ, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, Li W, Tung N, **Armstrong A**, Delaloge S, Bannister W, Goessl C, Degboe A, Hettle R, Conte P. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial.

Eur J Cancer. 2019 Oct;120:20-30. https://doi.org/10.1016/j.ejca.2019.06.023.

Health related quality of life was consistently improved for patients treated with olaparib, compared with chemotherapy of physicians choice.

Turner NC, Alarcón E, **Armstrong AC**, Philco M, López Chuken YA, Sablin MP, Tamura K, Gómez Villanueva A, Pérez-Fidalgo JA, Cheung SYA, Corcoran C, Cullberg M, Davies BR, de Bruin EC, Foxley A, Lindemann JPO, Maudsley R, Moschetta M, Outhwaite E, Pass M, Rugman P, Schiavon G, Oliveira M. BEECH: a dose-finding run-in followed by a randomised phase II study assessing the efficacy of AKT inhibitor capivasertib (AZD5363) combined with paclitaxel in patients with estrogen receptor-positive advanced or metastatic breast cancer, and in a PIK3CA mutant sub-population.

Ann Oncol. 2019 May 1;30(5):774-780. https://doi.org/10.1093/annonc/mdz086.

Capivasertib had no apparent impact on the tolerability and dose intensity of paclitaxel. Adding capivasertib to weekly paclitaxel did not prolong PFS in the overall population or PIK3CA+ sub-population of ER+/HER2- advanced/metastatic breast cancer patients.

Turner NC, Telli ML, Rugo HS, Mailliez A, Ettl J, Grischke EM, Mina LA, Balmaña J, Fasching PA, Hurvitz SA, **Wardley AM**, Chappey C, Hannah AL, Robson ME; ABRAZO Study Group. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline BRCA1/2 Mutations (ABRAZO).

Clin Cancer Res. 2019 May 1;25(9):2717-2724. https://doi.org/10.1158/1078-0432.CCR-18-1891.

Talazoparib, , is an orally available poly ADP ribose polymerase (PARP) inhibitor. Confirmed overall response rate was 21% for; cohort 1 and 37% cohort 2 and a median duration of response of 5.2 months thus showing activity in previously treated patients.

Armstrong AC, Clay V. Olaparib in germline-mutated metastatic breast cancer: implications of the OlympiAD trial.

Future Oncol. 2019 Jul;15(20):2327-2335. https://doi.org/10.2217/fon-2018-0067.

The PARP inhibitor Olaparib, has recently been evaluated in the Phase III OlympiAD trial, and demonstrated a significant progression-free survival advantage in patients with HER2-negative metastatic breast cancer and a germline BRCA-mutation. This article reviews the findings and potential implications of the trial.

Turner NC, Telli ML, Rugo HS, Mailliez A, Ettl J, Grischke EM, Mina LA, Balmaña J, Fasching PA, Hurvitz SA, **Wardley AM**, Chappey C, Hannah AL, Robson ME; ABRAZO Study Group. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline BRCA1/2 Mutations (ABRAZO).

Clin Cancer Res. 2019 May 1;25(9):2717-2724. https://doi.org/10.1158/1078-0432.CCR-18-1891.

Talazoparib exhibited promising antitumor activity in patients with advanced breast cancer and germline BRCA mutation.

Robson ME, Tung N, Conte P, Im SA, Senkus E, Xu B, Masuda N, Delaloge S, Li W, **Armstrong A**, Wu W, Goessl C, Runswick S, Domchek SM. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer.

Ann Oncol. 2019 Apr 1;30(4):558-566. https://doi.org/10.1093/annonc/mdz012.

The oral poly(ADP ribose) polymerase (PARP) inhibitor olaparib in patients with a germline BRCAm and HER2-negative metastatic breast cancer (mBC) is equally active in patients with BRCA1/2 pathogenic variants and thus is an important choice of therpy in this group of patients.

Adams S, Loi S, Toppmeyer D, Cescon DW, De Laurentiis M, Nanda R, Winer EP, Mukai H, Tamura K, **Armstrong A**, Liu MC, Iwata H, Ryvo L, Wimberger P, Rugo HS, Tan AR, Jia L, Ding Y, Karantza V, Schmid P. Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study.

Ann Oncol. 2019 Mar 1;30(3):405-411. https://doi.org/10.1093/annonc/mdy518.

Pembrolizumab targets and blocks a protein called PD-1 which triggers anti-tumour T-cell activity. Pembrolizumab as first-line therapy for patients with PD-L1-positive mTNBC produced a disease control rate of 24% for a median of 10 months indicating some effectiveness.

4.3 Endocrine therapy

Howell SJ, Keevil B, Higham C, Owen LJ, Monaghan PJ. RE: Fulvestrant falsely elevates oestradiol levels in immunoassays in postmenopausal women with breast cancer.

Eur J Cancer. 2020 Sep;136:204-205. https://doi.org/10.1016/j.ejca.2020.04.050.

Commentary

Jones RH, Casbard A, Carucci M, Cox C, Butler R, Alchami F, Madden TA, Bale C, Bezecny P, Joffe J, Moon S, Twelves C, Venkitaraman R, Waters S, Foxley A, **Howell SJ**. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial.

Lancet Oncol. 2020 Mar;21(3):345-357. https://doi.org/10.1016/S1470-2045(19)30817-4.

Capivasertib (AZD5363) is a potent selective oral inhibitor of all three isoforms of the serine/threonine kinase AKT. Participants received fulvestrant plus capivasertib (n=69) or fulvestrant plus placebo (n=71) and progression-free survival was significantly longer in participants who received capivasertib than in those who received placebo.

4.4 Biomarkers

Turner NC, Kingston B, Kilburn LS, Kernaghan S, **Wardley AM**, Macpherson IR, Baird RD, Roylance R, Stephens P, Oikonomidou O, Braybrooke JP, Tuthill M, Abraham J, Winter MC, Bye H, Hubank M, Gevensleben H, Cutts R, Snowdon C, Rea D, Cameron D, Shaaban A, Randle K, Martin S, Wilkinson K, Moretti L, Bliss JM, Ring A. Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial.

Lancet Oncol. 2020 Oct;21(10):1296-1308. https://doi.org/10.1016/S1470-2045(20)30444-7.

ctDNA testing offers accurate, rapid genotyping that enables the selection of mutation-directed therapies for patients with breast cancer. The results demonstrate clinically relevant activity of targeted therapies against rare HER2 and AKT1 mutations, confirming these mutations could be targetable for breast cancer treatment.

Coombes RC, Page K, Salari R, Hastings RK, **Armstrong A**, Ahmed S, Ali S, Cleator S, Kenny L, Stebbing J, Rutherford M, Sethi H, Boydell A, Swenerton R, Fernandez-Garcia D, Gleason KLT, Goddard K, Guttery DS, Assaf ZJ, Wu HT, Natarajan P, Moore DA, Primrose L, Dashner S, Tin AS, Balcioglu M, Srinivasan R, Shchegrova SV, Olson A, Hafez D, Billings P, Aleshin A, Rehman F, Toghill BJ, Hills A, Louie MC, Lin CJ, Zimmermann BG, Shaw JA. Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence.

Clin Cancer Res. 2019 Jul 15;25(14):4255-4263. https://doi.org/10.1158/1078-0432.CCR-18-3663.

This study demonstrates that patient-specific ctDNA analysis can be a sensitive and specific approach for disease surveillance for patients with breast cancer. More importantly, earlier detection of up to 2 years provides a possible window for therapeutic intervention.

Rothé F, Silva MJ, Venet D, Campbell C, Bradburry I, Rouas G, de Azambuja E, Maetens M, Fumagalli D, Rodrik-Outmezguine V, Di Cosimo S, Rosa D, Chia S, **Wardley A**, Ueno T, Janni W, Huober J, Baselga J, Piccart M, Loi S, Sotiriou C, Dawson SJ, Ignatiadis M. Circulating Tumor DNA in HER2-Amplified Breast Cancer: A Translational Research Substudy of the NeoALTTO Phase III Trial.

Clin Cancer Res. 2019 Jun 15;25(12):3581-3588. https://doi.org/10.1158/1078-0432.CCR-18-2521.

ctDNA detection before neoadjuvant anti-HER2 therapies is associated with decreased pCR rates. Interestingly, patients with HER2-enriched tumors and undetectable ctDNA at baseline had the highest pCR rates, therefore appearing as the best candidates for treatment deescalation strategies.

Rothwell DG, Ayub M, Cook N, Thistlethwaite F, Carter L, Dean E, Smith N, Villa S, Dransfield J, Clipson A, White D, Nessa K, Ferdous S, Howell M, Gupta A, Kilerci B, Mohan S, Frese K, Gulati S, Miller C, Jordan A, Eaton H, Hickson N, **O'Brien C**, Graham D, Kelly C, Aruketty S, Metcalf R, Chiramel J, Tinsley N, Vickers AJ, Kurup R, Frost H, Stevenson J, Southam S, Landers D, Wallace A, Marais R, Hughes AM, Brady G, Dive C, Krebs MG. Utility of ctDNA to support patient selection for early phase clinical trials: the TARGET study.

Nat Med. 2019 May;25(5):738-743. https://doi.org/10.1038/s41591-019-0380-z.

Next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) supports blood-based genomic profiling. Actionable mutations were identified in 41 of 100 patients, and 11 of these patients received a matched therapy. These data support the application of ctDNA in this early phase trial setting and provides a practical template for bringing routinely applied blood-based analyses to the clinic.

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