

# BSHG News

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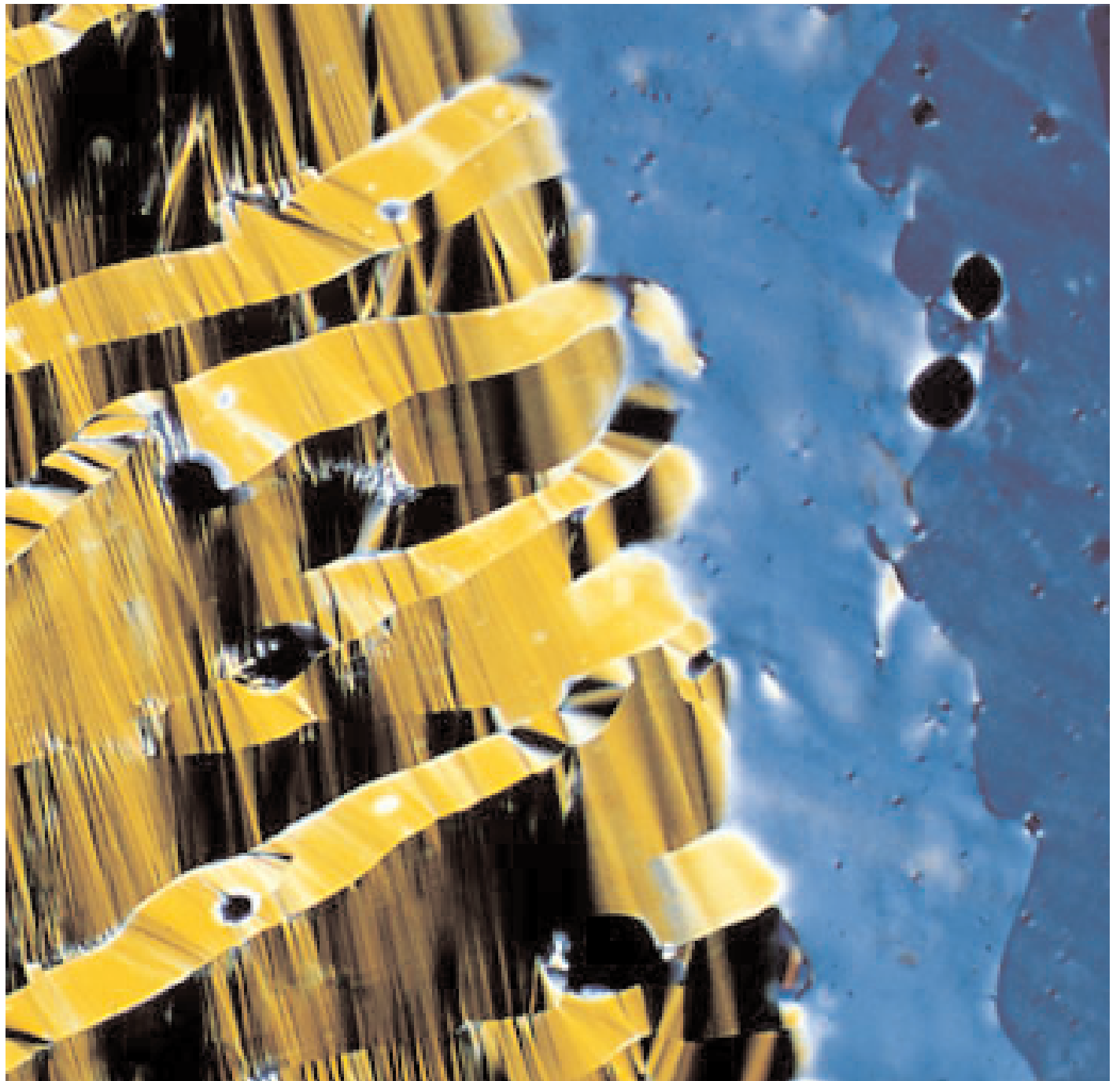
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# Editorial

Chris Jacobs

I have discovered that one of the more challenging aspects of the newsletter editor's role is getting in touch with the membership. Some, though I fear not many, of you will have received my recent email request for articles and information about studies and meetings. However, judging by the number of emails that were returned to me, my list was very out of date (or perhaps it was just that no one wanted to hear from me again!). A few people have kindly let me know their updated contact details. However, on behalf of CGG newsletter editors present and future, it would be a great help if everyone could let me know their current email addresses.

Thank you to all who have provided articles for this newsletter. Anneke Lucassen's lively account of her sabbatical in Amsterdam wasn't what I had originally envisaged for the 'spotlight on Southampton', but it provides an interesting and personal insight into the Dutch approach to cancer genetics. This is particularly topical in view of the rapidly approaching joint meeting with the CGG, the Dutch Cancer Genetics Group and the Psychosocial Aspects of Hereditary Cancer Dutch Psychological Society.

'Unclassified variants' feature strongly in this newsletter with an update from Ian Frayling on the recent Best Practice Meeting on Unclassified Variants and information from Gabriella Pichert and Jo Morris about a new study (AFFECT) looking at unclassified variants in the BRCA1 gene. We also have an update from Shirley Hodgson on the POET study and information about the about the BRCA Trial. Ian Ellis has updated us on

the exciting plans for the CGG website which will hopefully be up and running in the near future.

The team at UCLH have introduced their Preimplantation Genetic Diagnosis service for cancer. Other centres are likely to begin setting up similar services in the near future. PGD for adult onset cancer is an issue that will no doubt continue to be debated by all involved in cancer genetics, as well as in the media and amongst the general public.

The December CGG meeting at Guy's went very well, thanks to the wonderful organisational skills of Eileen (nee Connelly), who has recently become Mrs Eileen Bowley. The meeting provided an update to the many ongoing collaborative studies, several of which have been running for a number of years. It was especially interesting to hear how these studies are developing and to learn about the emerging findings. The case discussions, at which people are often rather reticent, stimulated some lively and thought-provoking discussion.

CGG members who are also AGNC members will no doubt have read the article about the Genetic Counsellors Statutory Regulation Steering Group in the AGNC section of this newsletter. To the non-genetic counsellors amongst you I apologise for the free advert. The GCSRSG is working on behalf of genetic counsellors in the UK towards recognition of genetic counselling as an independent and regulated profession. Statutory regulation would ensure that only accredited genetic counsellors would be able to practice under that title,

so that patients seeing a 'genetic counsellor' would be safe in the knowledge that the individual had the appropriate skills and training for the role. It also offers external codes of conduct and fitness to practice to develop and maintain the high quality of the profession. This is likely to be a long process and you can follow all the action (!) in the AGNC newsletter.

I hope you enjoy this section of the newsletter and will continue to send me your articles, comments, courses, study information and anything else you think might be of interest to your colleagues in cancer genetics. If there is anything you would like to see (or not see) in this section you can let me know when you send me your up to date email addresses!

# Spotlight on Southampton ....well ....by the Amstel....

Anneke Lucassen

Our new and energetic newsletter editor suggested that I write a 'focus on Southampton' slot for this newsletter. However, right now my finger has slipped slightly from the pulse of the latest Southampton activities since, thanks to the generosity of said place, I have been on sabbatical in Amsterdam since the beginning of March.

Some of you will know that I am Dutch, but I left the country as a littl'un in 1969, so have been in the UK long enough to be thoroughly anglicised. We were thrown in at the deep end. We found an apartment in central Amsterdam, two places at a local Dutch state school for two very 'Sarfampton' daughters and a sabbatical at NKI for English hubby.

The first thing I notice is how welcoming the Dutch are, both socially and professionally. Without fail all those who I've approached have enthusiastically arranged to meet and/or shown me round their department. Christi van Asperen in Leiden in particular has bent over backwards to show me Dutch cancer genetics. My initial impressions have been that it's pretty similar to the UK. However, like the trains perhaps, services seem a bit more streamlined and coordinated. You can find standardised information leaflets on websites like BRCA.nl, referral rates and attendance figures are nationally collated (but then it is a small country). The government perhaps also has had a greater say in what can and can't be done (no PGD allowed for adult onset cancers, for example) and I suspect the insurance-based healthcare also means that, rightly or wrongly, such care is a bit more

'patient centred'. For example, in the UK, I find myself often labouring the lack of evidence for mammography under 50 because, despite NICE, it's not readily available in all of the areas covered by the Southampton genetics service. My impression in The Netherlands is that above a certain degree of family history, mammography and even MRI are uniformly covered by insurance so it's just arranged and the lack of evidence does not loom so large.

My Dutch is being polished up nicely. Most of the medical terms of course have the same roots: "just lay the emphasis on the second syllable instead of the first and you'll have the Dutch pronunciation" I was told. So, "preventieve ablatio mammae" will not be a great mystery, likewise "Familiare Adenomateuze Polyposis". Or how about "de recessief-erfelijke ziekte myh-geassocieerde polyposis"? There's a prize to the first UK person who tells me what "Preventieve verwijdering van eierstokken en eileiders" might mean. That said, I went badly wrong in assuming that 'collaboratie' meant collaboration. It does technically, but the Dutch term is reserved solely for Nazi sympathizers in WW2.

Living in Amsterdam is refreshingly easy going. Despite the worries of some Southampton neighbours, we have not entered a den of prostitution and drug soaked debauchery (but yes, you can smell the 'coffee' shops everywhere). If anything, life feels somewhat safer here than it does in Southampton, a fact I attribute in large part to the lack of cars on the tiny canal lined streets. It really is quicker to go by bike and, as its all flat

even my 8 year old daughter can cycle for miles on end. It's true that to get anywhere you have to learn to cycle assertively but I've not witnessed any of the road rage or motorists-shouting-abuse-at-cyclists that I've experienced cycling to work in the UK. At school the kids seem to be given independence at an earlier stage: teachers let them find their boundaries by themselves rather proscribe them. As a consequence, maybe the kids take more responsibility for their actions. My daughters' school is a noisy and boisterous place, rather intimidating and scary on first impressions, but the children are all friendly and courteous and my daughters feel very welcome (even though their Dutch progresses slowly as everyone wants to practice their English on them).

I'm reminded of Raoul Hennekam's surprise at the lack of composting in the UK (BSHG newsletter a few issues back-ability to compost-genetic or environmental Raoul?) I sense that the Dutch are good at corporate responsibility. You soon get used to taking your own carrier bags to the supermarket when there isn't a norm to pick up new ones each time you go.

Anneke Lucassen, back in the UK in August, meanwhile still on [annekel@soton.ac.uk](mailto:annekel@soton.ac.uk)

# Minutes of December 2007 CGG steering group meeting

Gareth Evans (Chair), Anneke Lucassen  
(Secretary), Ian Ellis (Treasurer)

## Forthcoming Conferences

1. Spring 2007: joint meeting with Dutch Cancer Genetics Group and international group Psychosocial Aspects of Hereditary Cancer in Manchester 22nd – 24th May.
2. Autumn 2007 – 7th December Guys
3. May 2008: Birmingham with BASO

## Recent meetings

1. One day meeting in December 2006 at Guys was very successful with summaries of ongoing research and clinical problems session.
2. Breakthrough Summit to address BRCA testing backlog attended by Andy Burnham Minister for genetics. Conclusion: backlog being sorted!

## Publications

1. 'hearsay' family history: consent in clinical practice and research: general statement about hearsay family histories in last BSHG newsletter
2. Direct to Consumer genetic testing. CGG to respond to ASHG draft statement on direct testing. Concern about context and validity. Concern that pressure from government to privatise 15% of pathology services may encourage DCT

## Newsletter Editorship and website

1. Chris Jacobs editor from 2007.
2. Current CGG website on Cambridge server and does not allow for online abstract submission. Rajesh (BSHG) commissioned to upgrade and make closer links with BSHG.

## Ongoing issues

1. BRCA patent. Myriad appealing to overturn rejection of patent for BRCA1. Gert Matthijs, Belgium asking for money to support legal fees. In principle £600 agreed, to discuss with BSHG.
2. MRI screening guidelines from NICE have been published. Issues re funding around the country. Lots of centres are having difficulties with commissioning.

# An update on the Cancer Genetics Group Website

Ian Ellis

Work on the CGG website is ongoing. There will be seven areas or main pages to the website:

Page one will be the welcome page with links to the other CGG pages. The home page will enable navigation to news, updates, headlines, editorial and significant trials' results and such like.

Page two will have news, updates, headlines, editorial, headlines and major developments, significant trials' results and articles from the CGG section of the BSHG newsletter.

On page three you will find CGG steering group news, including reports and contact details. This page will also include important news and reports, plans for the future and an application system for CGG membership.

Page four will include details of CGG Meetings as well as related scientific and clinical events with details of forthcoming CGG meetings. There will be a section for publicising forthcoming scientific and clinical meetings.

On page five you will find research related to CGG, interests with ongoing research projects as a database with brief details, web-links, E mail and contact details of researchers involved.

Page six will include relevant documents. This may include the actual document or the web-links to the documents or policies of interest to CGG members.

Finally, on page seven you will find details of the next CGG meeting and links to the BSHG York meeting. Hopefully, on line submission of abstracts for future meetings and registration for delegates will be possible. This page will enable meeting announcements to be made and possibly enable specific documents and selected PowerPoint presentations from the meeting to be made available.

# Best Practice Meeting on Unclassified Variants: NOWGEN, 12-13 April

Ian Frayling

An excellent two day meeting was held in Manchester, courtesy of the National Genetics Reference Laboratory (Manchester) and under the auspices of the CMGS, with representatives from most NHS laboratories together with laboratory colleagues from The Netherlands and other European countries, on the burgeoning subject of the interpretation of so-called 'unclassified variants'.

As it becomes easier to sequence genes, so more mutations are being found, the significance of which is uncertain. Of course, this can apply to any gene, but Professor Sean Tavtigian, building on his earlier presentation at the Winter CGG meeting, was able to expand on the methods that he and colleagues have started to apply, and will be able to apply in the future, to this difficult subject with the data available from Myriad and on the BIC database (<http://research.nhgri.nih.gov/bic/>) relating to BRCA1/2.

Many strands were brought together on the issues surrounding unclassified variants including, in no particular order, the importance of locus-specific databases (such as that organised by InSiGHT; <http://www.insight-group.org/>), and how the NHS DMuDB; (<http://www.ngrl.org.uk/Manchester/DmuDB.htm> might help in this); having not just reference sequences for genes, but also reference alignments of sequences from multiple species; how to add in data from e.g. tumour analysis, LOH, linkage etc; controls and quality standards; validation of softwares that predict the significance of splicing and amino acid changes and standardisation of reports between laboratories; RNA and functional studies etc. There are parallel efforts going on in Australasia and the US, and it is hoped to work with these initiatives to achieve a common set of guidelines.

There will be a detailed report from this meeting issued by the CMGS, but it is important for clinicians and counsellors to be aware of these developments so that they can best work with laboratory colleagues for the benefits of patients.

# Preimplantation Genetic Diagnosis for Cancer Predisposition

Joy Delhanty, Joyce Harper, Sioban SenGupta, Karen Fordham (UCL Centre for Preimplantation Diagnosis (PGD) and the Assisted Conception Unit, University College London Hospitals Foundation Trust)

Prenatal diagnosis for cancer predisposition is not widely reported and can be considered controversial as onset may be in adulthood, penetrance may be incomplete, treatments are available and in some cases prophylactic surgery to avoid cancer development is proposed. Preimplantation genetic diagnosis offers couples an alternative to pregnancy termination by the selection of embryos for implantation that are free from the predisposing germline mutation in that family. Diagnosis is based upon genetic analysis of a single cell biopsied from embryos created by IVF. World wide PGD has been reported for APC, retinoblastoma, NF1, NF2, MEN1, VHL and BRCA1.

The first successful cycles of PGD for cancer predispositions in the UK have been carried out in our centre. We have specialised in doing PGD for these relatively rare disorders. For this reason we have maintained our focus on direct mutation detection in order to be able to apply PGD to a wide spectrum of mutations in a range of cancer predisposing genes even for couples with de novo mutations. However we have also developed PGD protocols that can be applied to those families, with NF1 for example, where the presence of the germline mutation has only been established by haplotype analysis.

We are now licensed by the Human Fertilisation and Embryology Authority (HFEA) to offer treatments for mutations in the following cancer genes/disorders:

- Adenomatous polyposis coli (APC)
- Retinoblastoma (RB1)
- Neurofibromatosis Type I (NF1)
- Neurofibromatosis Type II (NF2)
- Li Fraumeni syndrome (TP53 gene)
- Von Hippel Lindau syndrome (VHL)

We are in the process of applying for licences for BRCA1 and MEN1 and we are developing protocols for HNPCC.

## Dealing with Referrals

Referrals may be sent to any of those named below. Couples will be offered a preliminary consultation with Karen Fordham, Clinical Nurse Specialist in PGD, normally within one month of receipt of the letter. If the couple is keen to proceed, sample collection will be arranged and, if appropriate, an application for NHS funding will be initiated. Funding is obtained for about half of PGD referrals. If the referral is not from a clinical geneticist, we will ensure that the couple receives genetic counselling before proceeding. Whilst the protocol is being developed, fertility checks will be carried out. Once the protocol is ready, couples will have a further PGD consultation where one of the scientists responsible is present as well as a consultation with a gynaecologist.

# Oncology for Geneticists

Diana Eccles

If you are working in cancer genetics and feel your knowledge of current developments in cancer treatment is a little rusty or incomplete, then this course is for you.

Geneticists (consultants and SpRs) and senior genetic counsellors/nurses who are working in the field of cancer genetics will find it most useful.

The emphasis will be on current day approaches to surgery and medical treatment of common cancers as these are applied to hereditary cancer cases.

## Course format

This is a one day course, mainly lecture style teaching from oncology and surgery specialists with Q&A sessions at the end of each major topic area.

## Venue

Southampton University Hospitals NHS Trust (overnight accommodation can be arranged at a local hotel if required).

## Cost

£50 per person per day including lunch, tea and coffee.

## Proposed date

29th November

For a provisional programme please email Carolyn.Goodwin@suht.swest.nhs.uk

Places will be limited to a maximum of 50 so please register interest early to avoid disappointment.

# Research update

Diana Eccles

## The AFFECT study

**Gabriella Pichert and Jo Morris**

A new study co-coordinated by geneticists from Guy's and St Thomas' Trust and King's College London has begun recruiting. The AFFECT study aims to examine breast cancer pathology and gene alterations in tumours of people who carry a BRCA1 unclassified variant.

### What is AFFECT?

This study aims to collect paraffin embedded breast cancer tissue, blood, clinical and family history information from carriers of unclassified BRCA1 gene variants in order to examine evidence for BRCA1-mediated tumourigenesis. It is funded by the Breast Cancer Campaign and Guy's & St. Thomas' Charity.

### Why do we need AFFECT?

Most of our understanding of the consequences of a dysfunctional BRCA1 gene comes from 'truncating' mutations. Despite the name, the majority of truncating mutations are not expressed but lost entirely through decay of the transcript.

As genetic testing protocols around the country change to a full genetic screen, many more individuals with unclassified BRCA1 gene variants will be identified. These types of genetic change are quite different to the 'truncating' class as they occur in the context of an expressed protein and may or may not have clinical consequences.

In a research setting an integrated multifactorial approach has been developed to help classify currently unclassified BRCA1 variants. However, an acknowledged assumption in this

approach is, that pathogenic variants that are expressed, result in the same molecular consequences as non-expressed 'truncating' mutations.

The AFFECT study aims to establish whether this assumption is correct. In addition, the study will address questions central to our understanding of the aetiology of breast cancer mediated by BRCA1 gene mutations.

### Why are we only looking at BRCA1 variants?

We focus on carriers of unclassified BRCA1 gene variants because their breast cancer pathology is thought to be predictive of BRCA1 germline mutation carrier status and because recently developed biochemical functional tests for the N- and C-terminus of the protein have the potential to estimate cancer risk if their results can be validated independently. Pathogenic BRCA1 N- and C-truncating variants will also result in an expressed BRCA1 protein.

### When does recruitment begin?

Recruitment to the AFFECT study has begun in London (Guy's Hospital and St Georges Hospital), Manchester and Birmingham and will begin soon in Southampton and Glasgow.

### Who can be recruited?

Carriers with the following BRCA1 gene variants who are affected with breast cancer:

- Any missense (with a change of amino acid) variant,
- Any in-frame insertion or in-frame deletion variant,

- BRCA1 185delAG and 188del11

- Variants: (5677insA, 5622C>T (Arg1835ter) 5382insC).

### How can patients be recruited?

If your centre is not yet involved, please contact a member of the study team. We will send you an introductory letter explaining how the study is set up. We will provide payment for each patient recruited and help you as much as possible with your ethics paperwork.

### Study contact details:

Dr Jo Morris (Chief Investigator - KCL)  
Email: jo.morris@genetics.kcl.ac.uk,  
Tel: 02071883699

Dr Gabriella Pichert (Principal Investigator – GSTT)  
Email: gabriella.pichert@gstt.nhs.uk Tel: 020718881398).

Ms Caroline Langman (Research Nurse)  
Email: caroline.langman@genetics.kcl.ac.uk Tel: 020718882603

# BRCA Trial Update

Andrew Tutt (Clinical Oncologist), Jessica Mozersky (BRCA Trial Patient Information Coordinator) and Navdip Sahota (BRCA Trial Coordinator)

## Trial Background

The BRCA Trial is a randomised phase II trial of Carboplatin compared to Docetaxel for confirmed BRCA carriers with metastatic breast cancer. It is based on the understanding of the specific DNA repair functions of the BRCA1 & 2 genes that suggests tumours lacking these proteins will be especially sensitive to chemotherapeutic agents containing platinum.

Women who carry mutations in BRCA1 and BRCA2 genes have an increased risk of up to 85% of developing breast cancer. The purpose of this trial is to assess whether Carboplatin alone is a safe and effective treatment of metastatic breast cancer in women who are BRCA1 and BRCA2 carriers. This will be compared to standard treatment with Docetaxel in terms of toxicity, response and time to progression. The trial aims to recruit 148 patients. All patients have the option of crossing over to the alternative treatment arm upon progression.

## UK Status

The BRCA trial now has 17 open centres in the UK, and more continue to come on board. There are 11 patients entered on the trial to date.

## International Collaboration

International collaboration is key to the success of this trial. We are extremely pleased to announce that a research nurse was appointed in April 2007 to work in Israel for 2 years. Israel is a particularly important site because of the high frequency of BRCA1 or BRCA2 founder mutations in Ashkenazi Jews (approximately 2.1%) compared to the UK general population (0.25%). Approximately 12% of patients developing breast cancer in Israel are BRCA1 or BRCA2 mutation carriers. The primary role of the research nurse is the overall coordination, identification and recruitment of eligible

patients at participating Israeli sites. In addition, the Royal Melbourne Hospital in Australia has recently opened the BRCA trial.

We are currently in the process of opening the trial in Canada, Germany, Portugal and Sweden.

## Increasing Awareness of the trial amongst BRCA carriers

This trial has been publicised amongst the health professional community, and we are now seeking ways to increase awareness of this trial amongst BRCA carriers. A poster has recently been designed in collaboration with BRCA carriers, breast care nurses and Breakthrough Breast Cancer. The poster will be made available to genetic, oncology and surgical clinics throughout the UK once ethical approval is obtained.

We have recently consulted with a sample of geneticists and genetic counsellors regarding the suitability of sending information on the trial directly to carriers. For interested genetic centres, we will develop information for BRCA carriers about this trial. If there are any suggestions regarding raising awareness of this trial amongst BRCA carriers please contact the trial team at [brca@ctc.ucl.ac.uk](mailto:brca@ctc.ucl.ac.uk)

## Trial Website

For more information on this trial you can visit our website at [www.brcatrial.org](http://www.brcatrial.org). A health professional website can be accessed via this site as well as our dedicated patient website which contains an online eligibility questionnaire.

## Chief Investigators

Dr Andrew Tutt (Consultant Clinical Oncologist) and Professor Max Parmar (Statistician/Head of Cancer Division MRC).

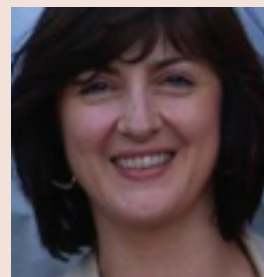
# The POET's Progress

Shirley Hodgson

The last six months, since we officially initiated this project, has been a steep learning curve for me, with initiation into the mysteries of the MHRA, EudraCT, SSA site-specific contracts, ethics, R & D and so on with vast amounts of paperwork. As yet we have not been able to recruit any women to the trial. I gather that this is not a unique experience, and that many similar trials have spent the first year of the project engaged in this bureaucratic process. We have now completed most of the background work and have designed a website (<http://poet.nameonthe.net/>), so recruitment should start in the next month or so.

We are very grateful to all our colleagues who have been so enthusiastic and encouraging, and we also have many international colleagues who are supportive and hope to join us when the UK part of the trial has started.

## CGG News Editors



## Deadline for contributions for next issue is Friday 5 October 2007

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