November 2003 NEWSLETTER

kConFab
Kathleen Cuningham Foundation
CONsortium for research into FAmilial Breast Cancer
www.kconfab.org phone (03) 9656 1542

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DEAR READERS,

kConFab has been running for six years and in that time we have developed a truly world-class resource into the study of familial breast and ovarian cancer. You may have seen in the media this year that kConFab was described by one of the leading medical researchers in the USA as 'the world's best resource on breast cancer'.

The major requirement for research into familial disease is information and biological specimens from a large number of families. For this reason the research projects that rely on kConFab, of which there are now 34, have only recently begun to bear fruit. We predict that in the next few years, research conducted around the world that uses kConFab material will have a major impact on our understanding of familial breast and ovarian cancer. This could not happen without your enthusiastic and continued support, for which we are extremely grateful.

Some of the projects that kConFab is supporting, such as the prospective psychosocial study, we believe are unique world-wide and so likely to have a major impact when they come to fruition. We are very keen to support more, large, prospective studies of this type and you will see in this newsletter that we are exploring the possibility of starting another one looking prospectively at natural variations in the ovarian hormone, progesterone, and risk of breast cancer. This would require an ongoing commitment from a cohort of kConFab participants prepared to give a sample of blood or urine every year. More information on this study is included inside. If you think you may be interested in participating in this study please return the tear off slip in the reply paid envelope. This is not a commitment, just an expression of interest, so we can gauge how many women may be interested in taking part.

The most important news of this year is that we secured funding from the National Breast Cancer Foundation, the National Health and Medical Research Councils, the State Cancer Councils of Australia and the Breast Cancer Research Association that will enable us to recruit a total of 1000 families, and to re-contact them on an annual basis to update our information on each family. Our ten dedicated research nurses have already started this annual follow up, and so if you have not heard from them recently, you probably will in the near future.

As of September 1st 2003, kConFab has completed collection of 710 families and collected 6369 blood samples. 605 families have been tested by the hospital laboratories for mutations in BRCA1 and BRCA2, and 171 families are known to carry mutations in these genes that substantially increase their risk of breast cancer. A major kConFab initiative this year has been to re-test 250 families for BRCA1 and BRCA2 mutations, using a more sensitive technique than has been used previously and not surprisingly this has identified a few mutations in families that had not been found before.

The collection of breast and ovarian tissue from women having prophylactic surgery continues to expand and this will provide a very powerful resource for looking at the early changes that might lead to breast and ovarian cancers. We are particularly keen to try to collect tissue samples at the time of surgery to enable us to look comprehensively at the gene expression patterns in their tumours. New data published this year from an American research group has shown that tumours that arise in families without BRCA1 or BRCA2 mutations probably fall into two distinct classes. This distinction, which can only be made by examination of tumours collected straight from surgery, may greatly help us to identify additional 'BRCA' genes which is a major goal of breast cancer research world-wide. If you are having prophylactic surgery, or surgery for a suspected tumour, and wish to donate some of the tissue to kConFab please contact your local kConFab research nurse before surgery so that she can make arrangements with the surgeon and pathologist.

I hope you enjoy the fifth kConFab newsletter, and once again thank you for your past and continued participation!

Georgia Chenevix-Trench,
Chair, kConFab Executive Committee

Personal story from Mrs. M

I was happy for kConFab to write of my experience for the newsletter as I see it as a way of informing other people that it is important to seek immediate medical action should things "not seem right". I also wanted to highlight how important the Family Cancer Service and research studies like kConFab have been for my family.

I have always known that my family was at high risk for developing breast and ovarian cancer. My father was 1 of 12 children. Every one of these 12 children that married has had a child who developed cancer later in life.

For me, I had very little warning that something was wrong. Twelve years ago I was cleaning the bathroom when I was overcome by a strong sensation that is hard to describe, but it left me feeling quite faint. I sat down for a few moments to regain my composure, then started cleaning again, but I still had that giddy feeling. I rang my gynaecologist immediately to see if I could get an appointment. My husband and I were off to the USA the next Friday for a holiday so I was keen to make sure that there was nothing wrong with me. I was lucky, as there had been a cancellation so the gynaecologist could see me immediately. I had put on a little weight in recent times and slowed down a little, but I put this down to mid-life change. After an examination and some tests, he organised for a total hysterectomy to be performed immediately, and he found ovarian cancer. I was very lucky, as the cancer was well encased and hadn't spread. I'll never forget his words to me after the operation "I knew you had ovarian cancer due to your appearance and if you had left this operation another week you may not have been so lucky – the cancer would have started to spread". He consulted other cancer specialists about what follow up treatment I should receive and the general consensus was that nothing further need be done. It is now twelve years down the track I still haven't had any problems, but each year I have a check-up and mammogram. Unfortunately my dear cousin was diagnosed with ovarian cancer at about the same time as me. It was too late for her by the time she had surgery, the cancer had spread and she passed away soon after.

My family has been seeing Prof Judy Kirk, who is based at the Familial Cancer Service at Westmead Hospital in Sydney for the past few years. Prof Kirk and her team has given me and my extended family advice about surveillance and strategies that may prevent or at least minimize the risk of breast and/or ovarian cancer within my family. Last year, my blood sample collected by kConFab was found on analysis to contain a faulty gene (mutation) associated with the development of breast and ovarian cancer. At first they found a change in the gene called ATM, but they weren't sure that this was the real culprit, so we waited for more tests and research to be done. Eventually the research team found a fault in a gene which we had heard about in the clinic – BRCA1. This seemed to be the cause of the problem for our family, and the additional testing provided by kConfab helped solve the problem. This research result then had to be confirmed in another blood sample from me, taken by Prof Kirk in the clinic and analysed by the laboratory at Westmead. Once the research finding had been confirmed in an accredited testing laboratory, the team at Westmead contacted me to explain the results and to offer testing for others in the family who were at risk. Although many were already involved in kConfab, this next stage of "predictive testing" needed to be done on a new blood sample, after individual genetic counselling. As a result of this genetic test result, my eldest daughter decided to have a prophylactic mastectomy (removal of normal breasts). A small cancer was found in her breast tissue but thankfully it was very small and after a course of chemotherapy she is very healthy and managing well. Our whole family is very pleased with the help that we have received from the team at the Westmead and kConFab. We can see that the research being done by kConFab is essential if we are to understand this disease and help families like ours who are are at high risk for developing cancer.

Left to right:
Assoc Prof Judy Kirk (Familial Cancer Centre Westmead Hospital, Sydney),
Dr Hanne Meijers (Rotterdam Family Cancer Clinic, The Netherlands)

Genetic Counsellors from Melbourne, left to right:
Ellie Lynch (Royal Melbourne Hospital),
Rebecca D'Souza (Royal Melbourne Hospital),
Tarli Hall (Monash Medical Centre),
Susan Fawcett (The Royal Childrens' Hospital)

KCONFAB FOLLOW-UP PROJECT

Principal Investigator Associate Professor Kelly Phillips
Peter MacCallum Cancer Centre, Melbourne.

The kConFab follow-up project has now been running for 2 years with over 3500 questionnaires sent out to date. We have mailed out a questionnaire to all kConFab participants recruited before October 2000 who indicated that they were happy to receive further information.

We are pleased to report that 70% of these questionnaires have been completed and returned. The questionnaire collects important information on your health and lifestyle, and also updates family information particularly if family members have been diagnosed with new cancers in the last 3 years.

Nearly 25% of our participants have registered a change of address or contact phone details since recruitment to kConFab. We are working hard to maintain contact with all our participants but we are also relying on you to help us. If you know of any family members who have moved in the last 3 years and may not have received this newsletter, could you please complete and return the change of address form included.

Our kConFab follow-up project is currently funded by the NHMRC but this funding will expire at the end of the year. We have reapplied to the NHMRC and other funding bodies to ensure that this valuable ongoing updating of your family information continues. If our applications are successful we hope that we can continue to send you a follow-up questionnaire every 3 years.

We now have 3 research assistants working on the study: Ailsa Stewart, Joanne McKinley and Prue Weideman which means that our toll-free telephone line is manned Monday to Thursday nights until 7pm. Please don't hesitate to call us if you have any questions or problems completing your questionnaires. We are happy to complete questionnaires over the telephone if you are having trouble filling them in.

The opt-out card included with our questionnaires provides you with an opportunity to withdraw from the follow-up study if you are unable to help us at this time.

Many thanks to all of you who have completed and returned your questionnaires. Remember that it is not too late to fill it in! If your form is still sitting in that pile of paperwork pull it out now and send it off. If you need another copy just give us a call on 1800 111 581. Your information is greatly valued by the entire kConFab research network.

Ms Prue Weideman
Clinical Follow-up Co-ordinator,
1800 111 581.

OBTAINING GENETIC TEST RESULTS

kConFab and the Family Cancer Clinics are different organizations

kConFab is a National consortium of researchers who are working to understand why breast cancer runs in some families. Some members of these families also attend Family Cancer Clinics, in Australia and New Zealand, where their risk of cancer is assessed. While kConFab and the Family Cancer Clinics work closely together, they are quite separate organizations: kConFab is involved in many research projects concerning genetic susceptibility to breast cancer and ovarian cancer, while the Family Cancer Clinics offer a medical service that includes genetic counselling, genetic testing and clinical advice.

Both kConFab and the Family Cancer Clinics carry out genetic testing

Families with a very strong history of breast and/or ovarian cancer are invited to contribute to kConFab's research after their family history has been assessed in a Family Cancer Clinic. A kConFab researcher (usually a nurse) contacts the family to find out information about relatives, both close and distant, including individuals who may not have attended a Family Cancer Clinic. Many of the family members who enrol in kConFab provide a research blood sample. A portion of the blood sample may be used to search for mutations (faults) in genes involved in breast cancer. This process is known as genetic testing. Mutation searching is a slow business, initially involving detailed and careful screening of BRCA1 (standing for breast cancer 1 gene) and BRCA2 (breast cancer 2 gene) for mutations (faults) that may cause the increased risk of breast cancer within the family.

Family Cancer Clinics may also take a separate clinic blood sample from a family member (usually the person in the family who has developed breast or ovarian cancer at the youngest age). This sample is sent for genetic testing to a Family Cancer Clinic laboratory accredited to carry out clinical genetic testing.

The Family Cancer Clinic laboratory may find a mutation before kConFab, or sometimes kConFab is first to find a mutation in a family. In many families, a gene mutation has not yet been found.

How do families find out the results of their genetic tests?

If the Family Cancer Centre laboratory finds a mutation in BRCA1 or BRCA2, they will report the result directly to their local Family Cancer Clinic. The Family Cancer Clinic, in turn, informs the appropriate family member(s), after genetic counselling. Often the family members themselves take on the task of letting others in the family know that genetic information has become available, though the Clinic may assist with this.

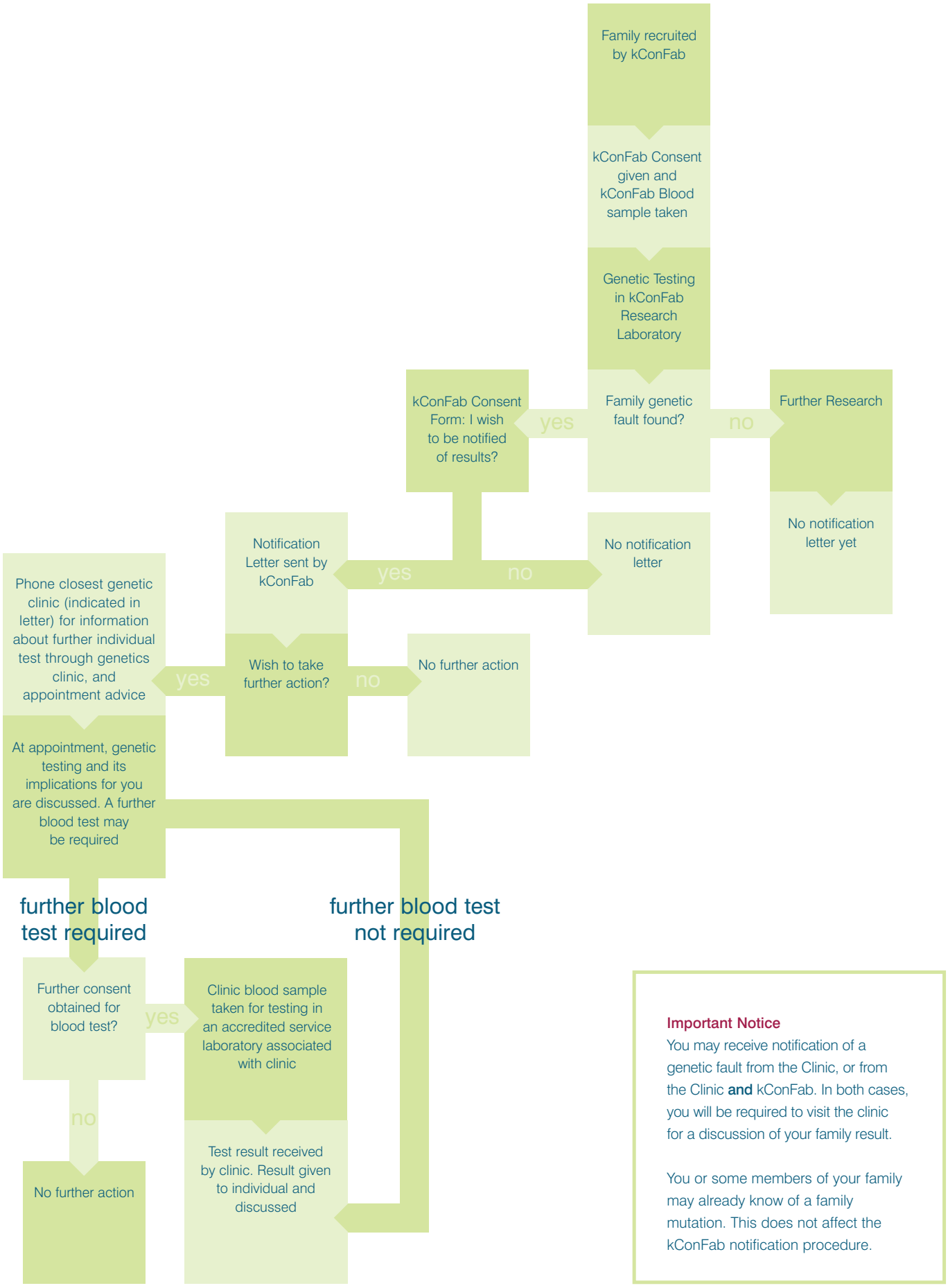
If kConFab finds a mutation, a different sequence of events is used to transmit the result. This is because kConFab is a research organization rather than a Family Cancer Clinic and therefore falls under different ethical rules. kConFab's project has been approved by Ethics Committees at many institutions. However, approval was given on condition that genetic information relevant to the family would be provided only through the Family Cancer Clinic system. When a mutation is discovered by kConFab, a letter is sent to all of the family members enrolled in the study, who wished to be informed, saying that information is now available that may be relevant to their health (or that of their family). kConFab is not allowed to inform individual family members about their own genetic testing results. However, enclosed with the letter is a list of Family Cancer Clinics where each family member may seek further information before considering whether they want to have a clinical genetic test. This is where the family moves out of the research study and back into the Family Cancer Clinic for appropriate counselling and with a new clinical blood sample being sent to an accredited testing laboratory. Once a mutation has been found in a family member, it is quite simple to test other members of the family to see if they carry the same mutation. The results of this type of genetic test should be available fairly quickly – generally within a month or two, but only through a Family Cancer Clinic.

Message from the kConFab team

So as to keep kConFab running smoothly, we would greatly appreciate if you would remember the following:

- Because family members are notified by mail, it is very important to keep your contact details up to date. We may even ask you to send us the name of another contact person, in case we are unable to find you. Some family members may have told us that they do not wish to be notified if kConFab finds a mutation. These people will not receive a letter.
- **Please remember that fresh surgical specimens are extremely valuable to research. Please ring your local kConFab research nurse to inform them of any new cases of suspected cancer in your family.**
- Ring the cancer specialist at your Family Cancer Clinic to inform them of any new cases of cancer in your family.
- **Please tell your research nurse if you change your address.**

Obtaining individual genetic results from kConFab



Important Notice

You may receive notification of a genetic fault from the Clinic, or from the Clinic **and** kConFab. In both cases, you will be required to visit the clinic for a discussion of your family result.

You or some members of your family may already know of a family mutation. This does not affect the kConFab notification procedure.

EXPERIENCES OF RECEIVING GENETIC TESTING RESULTS
IN WOMEN WITHOUT CANCER

Some results from the kConFab psychosocial study

As part of the kConFab Psychosocial Study, we interviewed women without breast cancer regarding their experiences of receiving results for hereditary breast / ovarian predisposition genes between one month and five years ago.

We asked about:

(a) the impact results had on themselves, and their immediate and extended family relationships;
(b) any advantages and/or disadvantages of receiving results and
(c) any changes in lifestyle made as a consequence of the test result.

Initial response to the result

Women described varying responses when they first received results, including intense feelings of shock, distress and guilt, while for others it was relief and acceptance. The initial emotional impact was surprisingly similar for both a positive and a negative result, although the thinking behind the reaction was different. For example, relief for women with a mutation-negative result was for themselves and their children; whereas relief for women with a mutation-positive result related to the removal of uncertainty, having their own self-image of being at risk validated and feeling a greater sense of control. However, a proportion of women within both groups expressed even initially, a strong sense of acceptance, based on having seen other family members coping with cancer. Thus, any test result (positive or negative) resulted in a short period of emotional turmoil for most but not all women.

Longer term response

Most women confirmed long-term advantages and cited no disadvantages to knowing their mutation status. Those with a mutation-positive result were reassured that they could take decisive steps to reduce their risk (i.e. screening/surgical options). Knowing their mutation status was described as empowering, and providing an opportunity to prepare emotionally and mentally for a potential cancer diagnosis. Indeed, some women, particularly those who were younger, reported that the mutation testing experience had generated important and positive life changes. Moreover, they felt future generations could benefit from this knowledge.

Most women who received a mutation-negative result felt a new peace of mind and a sense of normality. As one women said, “I now feel part of the normal population.”. However, some women who were mutation-negative, said that the results had not changed their sense of being at risk and reported that they had gone ahead with prophylactic mastectomy regardless. Other women reported they felt a need for continuing careful screening.

More than half the women reported supportive responses from other family members. Eleven mutation-negative women reported positive responses such as delight, happiness and relief on sharing the news. “They were excited as most of the immediate family were positive.” Communication was harder if the result was mutation-positive. A mutation-positive woman said: “I found it hard to tell my mother. They were disappointed for me but they were very supportive and said they would be there for me.”

Many women described difficulties or concerns about communicating with their family about genetic test results and subsequent decisions (such as prophylactic surgery). Complicating this is the reality that often multiple members of a family undergo testing, sometimes at the same time, sometimes alone, and with varied results. This of course results in a complex interplay of different reactions among family members, as test results for different family members are received. A mutation-positive women reported: “My elder brother who doesn’t have it asked if I hated him. I said no. He’s feeling guilty. My youngest brother felt better as he wasn’t the only one, but he felt angry about getting it.”

Another woman reported feeling worried that her in-laws would regard her as a “dud”. This response illustrates the difficulties in communicating not only with the biological family, but with the wider family circle – especially about such a complex, emotional topic. Members of the wider family (including partners) may have a “stake” in the results on the behalf of shared children/grandchildren, but often have not lived with cancer, as have the woman’s biological family, and so have less knowledge and experience to fall back on in adjusting to the results.

Being prepared for such difficulties, and the rippling effects within the family of obtaining test results, may promote better communication around this issue.

SURGICAL OPTIONS FOR WOMEN AT HIGH RISK OF BREAST CANCER

Professor Christobel Saunders, breast cancer surgeon, Perth.

Knowing you have a high chance of developing breast cancer due to a very strong family history of the disease, with or without a known gene mutation, is an incredibly frightening experience. Knowing what to do about it can be even more daunting.

For some women the option of "risk reduction surgery", as it is rather euphemistically known – bilateral mastectomy plus or minus reconstruction in practical language – is the best way to deal with the situation. For those women who opt for this, some recent research can give reassurance on two fronts – firstly it is likely to reduce the risk of developing breast cancer by a substantial percent and secondly women who go through with this option are, by and large, satisfied with their choice.

Evidence for the effectiveness of bilateral "prophylactic" mastectomy in high risk women has been shown in two recently published studies. One is from Hanne Meijers, a geneticist in Rotterdam, who presented her results at the recent kConFab scientific meeting in Queensland. Her group showed that no women carrying a breast cancer gene who chose to have this surgery developed breast cancer, whilst a number who carried the gene and opted for screening only, did go on to develop the disease. Confirmation by an American group at the Mayo clinic leads us to further confidence in this procedure.

But what about a woman's feelings after this kind of surgery? Well obviously every individual is different, but some comfort can be drawn from the findings of a UK group led by Mel Hatcher and Lesley Fallowfield who found that women who chose surgery were less likely to be anxious long term than those having screening only and that sexual functioning was the same for both groups.

So what does the procedure actually involve? Essentially once a woman decides to go down this path, she should have the opportunity to discuss surgical alternatives with a breast surgeon, a trained nurse counsellor and, if appropriate, a plastic surgeon. Options include removing breast tissue (usually with the nipple), a bilateral simple mastectomy, or this combined with reconstruction. Breast reconstruction aims to recreate the shape and volume of normal breasts, but they are NOT replacement breasts. A wide variety of techniques are available from simple implants under the chest wall muscles to much larger operations involving moving some of the "excess" skin, fat and muscle from one area of the body to the chest. Different procedures may be suitable for different women and a good first step is to discuss this with the surgeon, as one option may not suit an individual due, for example, to other medical conditions. Ask to see pictures and the surgeons results! It may be worth doing some further reading to decide which operation suits you best – I often recommend an American book A Woman's Decision: Breast Care, Treatment and Reconstruction (Quality Medical Home Health Library) by Karen J. Berger and John, III Bostwick (ISBN: 0312182295). Web sites giving both "medical" details and patients anecdotes can also be useful.

Finally, speaking to another woman who has gone through this experience will help many women decide – your local Cancer Helpline (13 11 20) can put you in touch with other women.

Whatever you decide – to have surgery or not, to have reconstruction or not – make sure you are comfortable with the medical team giving you advice and treatment. Be as well informed as possible. **Information is power!**

Left to right:
Dr David Callen (Scientist, Adelaide),
Prof Christobel Saunders (Breast Surgeon, Perth),
Dr Georgia Chenevix-Trench (Chair, Executive Committee, kConFab)

Above:
Dr Paul Meltzer
(invited speaker at kConFab conference from the National Institute of Health, USA)

kConFab PSYCHOSOCIAL STUDY

The kConFab Psychosocial Study is examining the role of life event stress, social support and other common psychological states such as anxiety and depression in the development of breast cancer. The study is being conducted from the Department of Psychological Medicine at the Royal North Shore Hospital, Sydney. Recruitment began in mid 2001, in conjunction with the Psycho-Immunology Study (now completed) and the Clinical Follow-up Study. The National Health and Medical Research Council of Australia has provided funding for 2001-2003 and we are in the process of applying for ongoing support.

This research has grown from a common belief that stress and other psychosocial factors may affect the risk of developing cancer, in particular breast cancer. It is unclear from existing research whether psychosocial factors such as stress can clinically alter cancer risk; and if so over what sort of time frame. The Psychosocial Study provides a unique and important opportunity for us to understand more about how these factors may influence the risk of developing cancer and how psychosocial risk factors may interact with familial and other risk factors. In addition, this study provides the potential for identifying specific risk factors that may be modified to reduce individual cancer risk.

We have now recruited over 800 women for this study (thank you to everyone who is participating). Both new and existing kConFab women who do not have cancer are being invited to participate. Participation involves completing a questionnaire about emotional responses, thoughts and feelings, and social support. We also request a telephone interview in which we ask about recent situations of stress or change (this usually takes about 45 minutes). Sometimes these situations are related to cancer, but just as often we hear about various sources of stress, related to relationships, other health issues, work, finances, and other aspects of life. We are planning to interview participants every 3 years, to make sure we are up-to-date with what is going on in people's lives. Those of you who joined this study right at the beginning, in the year 2001, will be hearing from us in 2004.

While the outcome of the main study questions are years away (we plan to follow everyone for at least 10 years), we do have some results of a small survey about the impact of receiving genetic testing results.

Our team works flexible hours, enabling telephone interviews to be conducted days, evenings and weekends, around participant's family and work commitments. If you have any questions or require assistance with any part of this study, please call our toll free numbers at Royal North Shore Hospital on 1800 772 838 (Australia) or 0800 888 340 (New Zealand).

Dr Melanie Price
Coordinator, Psychosocial Study
1800 772 838 (Australia)
0800 888 340 (New Zealand)

YOUR INFORMATION AND YOUR PRIVACY

By Sandra Picken, kConFab Data Manager

When you consent to participating in the kConFab study, we collect a large amount of information from and about you including your contact details, your medical history, any treating doctors and treatments undertaken, your family history and your dietary information. We also collect information about your blood and any other samples you kindly donate.

All of this information is stored in the kConFab Information System, known as "the database". The database currently stores full information on about 7000 consented participants. By law, we can only store in the database the gender, position of the person in the family tree, whether the person is alive or deceased, and whether or not the person is or was affected with cancer.

Where is the database located?
The database is housed at the Peter MacCallum Cancer Centre and is kept under lock and key. The information in the database is protected from misuse or damage by IT security which include password-protection and user authentication.

Who has access to my information?
Properly authorised and skilled kConFab Data Managers have full access to your information. In order to maintain and update your record, the Research Nurse who recruited you has access to the information you supplied to him or her, and the kConFab laboratory staff have access to the information about your blood and tissue samples.

All kConFab staff who have access to participant information are bound by the laws set out in the Privacy Act, 1988 (Commonwealth) as well as the privacy policy of the hospital where they are located.

Who can request access to my information?
Ethically approved, peer reviewed and fully funded research projects are able to obtain information on consented kConFab participants, but even then information is de-identified. No researcher will ever know your name, family name, or contact details.

Occasionally, kConFab will match your record to an external source, such as Australia Post or a Cancer Council register, in an effort to keep your records as accurate and up-to-date as possible. In these instances, your information may be identifiable (that is, contain your name and address). Only the information deemed necessary to make the match, such as name and last known address for Australia Post, will be released. These bodies are professional organisations bound by the same privacy principles as we are and can face penalties for any disclosure of your information.

Information can only be supplied to the health care professionals you identify and consent to access on your consent form. Your family members cannot access your information, unless you have given specific consent.

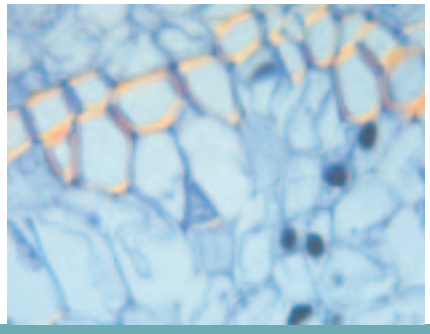
kConFab data is not for sale! No commercial body can purchase your information, as this would be in breach of the study's ethics at every level, as well as breaching privacy laws.

Some organisations, such as the Police, have a statutory right to information if it is relevant to their functions although this issue hasn't come up yet!

What about insurance companies, and other bodies, who may try to access my health or genetic test information? Information can only be supplied to insurance companies, employers, or other such bodies if you provide a signed consent or general release for those bodies expressly giving them permission to approach us. If a request is received from such a body without a signed general release from you, then it will be rejected and we will neither confirm nor deny any knowledge of you. If these requests are made to kConFab with your consent, we will contact you and recommend that this information is best sought from your health care professionals as they are in the best position to advise about your health status.

For further information regarding insurance issues and genetic testing, call the Investment and Financial Services Association on (02) 9299 3022 (Sydney) or at their website www.ifsa.com.au or The Centre for Genetics Education on (02) 9926 7324 (Sydney) or at www.genetics.com.au. In New Zealand insurance associates have similar codes, and guidelines are also available from the Human Rights Commission, on 0800 496 877, or at http:/www.hrc.co.nz

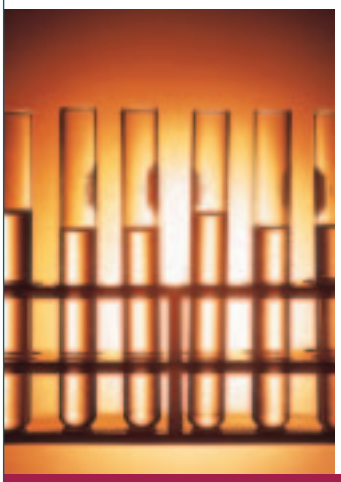
For further information on the kConFab database, please contact your kConFab Research Nurse.



RESEARCH PROJECT UPDATE

Dr Mandy Spurdle, QIMR, Royal Brisbane Hospital, Brisbane

While DNA 'faults' (mutations) in the BRCA1 and BRCA2 genes that result in truncated proteins usually increase the risk of breast cancer considerably, it is more difficult to predict the effect of DNA variation that results in more subtle (non-truncating) differences in protein structure. Such "unclassified variants" constitute ~15% of all rare DNA variants detected in kConFab breast cancer families, and yet their role in breast cancer remains unclear. We have recently undertaken a collaborative research project with Drs Chenevix-Trench (QIMR), Brown (University of Queensland) and Southey (University of Melbourne) to assess whether BRCA1 or BRCA2 'unclassified variants' cause breast cancer in such families. The study involves tracking the association between disease and presence of the variant within families, and assessing the effect of the DNA variant on function of BRCA1 or BRCA2 using a variety of laboratory tests. To date we have begun studies on 4 variants in BRCA1, and 10 variants in BRCA2. Our results suggest that at least 5 of these variants are unlikely to be deleterious (cause cancer) since they occur commonly in individuals without cancer, and/or do not track with the cancer in the family within which they were identified. To further establish the risk of developing cancer if you carry one of these unclassified variants, we have initiated experimental tests to test their function.



Even amongst carriers of known disease-causing BRCA1 or BRCA2 mutations, there are differences in age at onset of breast cancer, response to therapy, and other outcomes. A better understanding of the genetic and environmental factors that alter the clinical outcome for carriers of BRCA1 and BRCA2 mutations would improve counselling for BRCA1 and BRCA2 mutation carriers, and their family members. In addition, knowledge of the interaction of these genetic modifiers with environmental risk factors may lead to better advice regarding preventative measures, including lifestyle and pharmacological interventions, and assessment of suitability for radiation therapy. It is hypothesized that common DNA variants in other genes of the hormonal and DNA repair pathways may modify the expression of BRCA1 and BRCA2 mutations. In collaboration with other researchers, we have been assessing the effect of such common variants on age at onset of breast cancer amongst 180 mutation carriers from families recruited through kConFab, other Australian studies of breast cancer, and the UK EMBRACE study. We have shown that, in contrast to data from another research group, a common polymorphism of the androgen receptor gene does not appear to alter age at onset. In contrast, there is a suggestion that the AIB1 gene, previously reported to be associated with earlier age at onset of breast cancer in mutation carriers, may alter risk amongst BRCA1 mutation carriers. We thus plan, as part of an extended collaboration, to screen this marker in another sample of mutation carriers to confirm our finding.

Dr Melissa Brown, University of Queensland, Brisbane

Our research group is interested in how abnormalities in the BRCA1 gene causes breast cancer. To do this we are studying the initial changes that occur in breast cells containing abnormal forms of this gene. We have found that in these cells, the proteins that help cells to correctly orientate themselves and to correctly adhere to neighbouring cells are abnormal. We believe that abnormalities in these processes may contribute to cancer development in BRCA1 mutation carriers by allowing cells to manoeuvre themselves away from their normal position. A pilot study of tumour samples collected by kConFab supports this idea, with BRCA1 tumours also having abnormalities in these orientation and adhesion proteins.

THE PATHOLOGY OF BREAST CANCER IN WOMEN WITH ATM GENE VARIANTS

Associate Professor Judy Kirk and Dr Rosemary Balleine, Westmead Hospital, Sydney

This study, which commenced in March 2003, is examining the microscopic appearances of breast cancers that have arisen in families carrying certain variants in the ATM gene. The overall aim of this work is to determine whether breast cancers in these individuals have distinctive features compared with cancers that occur in other women. This may give insight into whether, and in what way, these particular genetic changes play a role in causing breast cancer. The study is being conducted at Westmead Hospital in Sydney in conjunction with investigators from other states of Australia and with the support of kConFab.

SEEKING EXPRESSIONS OF INTEREST FOR AN IMPORTANT STUDY

IF YOU ARE

- interested to learn about your hormones and menstrual cycle
- female who has not had breast or ovarian cancer
- willing to contribute to a study for the next 3-10 yrs
- prepared to have a mammogram, urine and blood tests

THEN WE WOULD LOVE TO KNOW WHETHER YOU MIGHT BE INTERESTED IN A NEW STUDY!!

The ovaries and the hormones they produce throughout reproductive life play a big role in the development of the breast, and also in breast cancer risk. But it is still not clear how these hormones interact with genetic, environmental and other factors to increase breast cancer risk. Recently, it has been shown that women taking combination estrogen/progestogenic HRT (hormone replacement therapy) have an increased breast cancer risk that seems to be related to the progestogenic component. What is urgently needed now are prospective studies, and kConFab is ideal for this because of the large cohort of women at increased risk of breast cancer. We are in the planning stages for a new study, to examine whether susceptibility to breast cancer is affected by individual differences in the activity of progesterone. We would do this by looking for variations in genes known to be involved in progesterone activity, associating these with individual variations in aspects of the reproductive system that are regulated by progesterone, and linking these with risk of breast cancer. To do this, we would ask kConFab participants to volunteer to work with us in a long term project aimed at understanding individual genetic variation in specific aspects of their reproductive cycles. The measures we would be looking at would include analysis of genetic variations in blood, breast density variations on mammograms, and progesterone transformation as measured in urine. We would also ask about mastalgia (breast pain during the menstrual cycle).

We anticipate that this study, if we have enough interest in it to get it going, will run for at least three years, and probably as long as ten years. The commitment that we would seek from each participant may include obtaining a mammogram, estimating mastalgia and giving blood and urine samples. Any volunteer could of course cease their participation in the study at any time.

So, we are now seeking expressions of interest so that we can estimate whether there would be enough participants within kConFab to carry out this study effectively. If you think you may be interested, please return the tear-out slip by December 15th 2003. This is not a formal commitment, just an indication for us whether we should proceed with this study.

We cannot begin this study unless we know there are willing participants so please return the slip below in the reply paid envelope if you may be interested.

Thank you!

TEAR OFF HERE

I would be interested in finding out more about the new proposed study and may wish to participate.

Name: _____

Address: _____

_____

Post code: _____

Telephone: _____

PLEASE PLACE THIS SLIP IN THE SUPPLIED REPLY PAID ENVELOPE

YOU'RE INVITED TO

BCNA'S 2ND NATIONAL BREAST CANCER CONFERENCE FOR THOSE WHO HAVE EXPERIENCED BREAST CANCER
THE MELBOURNE CONVENTION CENTRE
AUGUST 27TH–29TH 2004

Details in the December issue of 'The Beacon' and at www.bcna.org.au or on freecall no. 1800 500 258
Please mention that you are a 'kConFab' member.

If you would like to receive BCNA's quarterly free newsletter 'The Beacon' please ring 1800 500 258.
or contact BCNA's kConFab Community Representative Gerda Evans at gerda@bigpond.net.au

COLLABORATING FAMILY CANCER CENTRES

Melbourne
Familial Cancer Centre
Peter MacCallum Cancer Institute
St Andrews Place
East Melbourne, 3002
Contact: Ms Mary-Anne Young
Phone: 03 9656 1199
KConFab research nurse:
Beth Spear
Phone: 03 9656 1903

Royal Melbourne Hospital
Familial Cancer Centre
Parkville, 3050
Contact: Dr Geoffrey Lindeman
Phone: 03 9342 7151
KConFab research nurse:
Phone: 03 9342 4257

Victorian Clinical Genetics Service
The Murdoch Institute
Royal Children's Hospital
Parkville
Contact: Dr Mac Gardner
Phone: 03 8341 6293
KConFab research nurse:
Phone: 03 9342 4257

Victorian Clinical Genetics Service
Monash Medical Centre Clayton
Contact: Ms Tarli Hall
Phone: 03 9594 2026
KConFab research nurse:
Beth Spear
Phone: 03 9656 1903

Sydney
Familial Cancer Service
Department of Medicine
Westmead Hospital
Westmead, 2145
Contact: Assoc.Prof. Judy Kirk
Phone: 02 9845 6947
KConFab research nurse:
Bronwyn Harris
Phone: 02 9845 6845

Prince of Wales Hospital
Hereditary Cancer Clinic
High Street
Randwick, 2031
Contact: Dr Kathy Tucker
or Ms Karen Robinson
Phone: 02 9382 2577
KConFab research nurse:
Helen Conlon
Phone: 02 9382 2607

St George Community Hospital
Hereditary Cancer Clinic
Kogarah, 2217
Contact: Dr Kathy Tucker
Phone: 02 9382 2577
KConFab research nurse:
Helen Conlon
Phone: 02 9382 2607

St Vincent's Hospital
Family Cancer Clinic
Darlinghurst, 2010
Contact Dr Robyn Ward
or Rachel Williams
Phone: 02 8382 3395
KConFab research nurse:
Bronwyn Harris
Phone: 02 9845 6845

The John Hunter Hospital
Hunter Valley, NSW
Contact: Dr Tracey Dudding
Phone: 02 4985 3132
KConFab research nurse:
Helen Conlon
Phone: 02 9382 2607

Brisbane
Queensland Clinical Genetics Service
Royal Children's Hospital
Bramston Terrace
Herston, 4029
Contact: Dr Mike Gattas
Phone 07 3253 1686
KConFab research nurse:
Vivianne Geldard or Vicki Fennelly
Phone : 07 3636 5200

Adelaide
South Australian Clinical Genetics Services
Women's and Children's Hospital
North Adelaide, 5006
Contact: Dr Graeme Suthers
Phone: 08 8161 7011
KConFab research nurse:
Meryl Altree
Phone: 08 8161 6821, or,
Susan Schulz 08 8161 6393

Perth
Genetic Services of Western Australia
King Edward Memorial Hospital
374 Bagot Road
Subiaco, 6008
Contact: Dr Ian Walpole
or Prof. Jack Goldblatt
Phone 08 9340 1525
KConFab research nurse:
Anna Nash
Phone: 08 9340 1610

Tasmania
The Royal Hobart Hospital
The Lauceston General Hospital
The North West Regional Hospital, Bernie
Contact: Dr David Amor
c/o VCGS Royal Children's Hospital
Melbourne, 3002
Phone: 03 8341 6300 or
Dr Jo Burke
Royal Hobart Hospital
Phone: 03 6222 8296
KConFab research nurse:
Phone: 03 9342 4257

Auckland – New Zealand
Northern Regional Genetics Services
Auckland Hospital
Auckland, New Zealand
Contact: Dr Ingrid Winship
Phone 64 9 3737599 ext 3768
KConFab research nurse:
Jane Wylie
Phone 64 9 307 7232

Wellington – New Zealand
Central and Southern Regional Genetics Services
Wellington Hospital
Wellington South
Contact: Dr Alexa Kidd
Phone 64 4 385 5310
KConFab research nurse:
Jane Wylie
Phone 64 9 307 7232

KConFab Co-ordinator
Heather Thorne
Peter MacCallum Cancer Centre
Research Division
Phone: 03 9656 1542
email:
h.thorne@pmci.unimelb.edu.au

USEFUL WWW SITES

KConFab – www.kconfab.org
National Breast Cancer Foundation – www.nbcf.org.au
Breast Cancer Network Australia – www.bcna.org.au
Breast Cancer Research Association Inc – www.breastcancerasn.au