

Information and Policies for Access to Data and Biospecimens

What is kConFab?

The Kathleen Cuninghams Consortium for Research into Familial Breast Cancer (kConFab) is a consortium of researchers from many different disciplines, including genetics, epidemiology, clinical oncology, surgery, molecular biology, psychology, statistics and pathology. It was established by Professor Joseph Sambrook at the Peter MacCallum Cancer Institute in Melbourne in 1995. Members are drawn from all over Australia and New Zealand. The aim of kConFab is to create a large genetic, biological, epidemiological and clinical resource that will enable researchers to answer important questions relating to familial aspects of breast cancer.

How is kConFab funded?

kConFab is currently funded by the Kathleen Cuninghams Foundation for Breast Cancer Research (now the National Breast Cancer Foundation) but in the past has received grants from the National Health and Medical Research Council (NHMRC) of Australia, the Anti-Cancer Council of Victoria, the Queensland Cancer Fund, the Cancer Foundation of Western Australia, the Cancer Council of South Australia, the Cancer Council of Tasmania and the Cancer Council of New South Wales. These grants fund the core activity of kConFab but from 1997 there have been linked research grants, funded by NHMRC and other agencies that depend on the kConFab resource. Further applications are encouraged from national and international researchers, whether or not they are members of kConFab.

How is kConFab organised?

The Principal Investigator on the Kathleen Cuninghams grant is Professor Stephen Fox who is therefore ultimately responsible for decision making. However, he is assisted by an Executive Committee, chaired by Professor Stephen Fox, and several sub-committees - Biospecimens, Ethics Reference Group, Mutation Review, Pathology, Translational Research and Database/Analysis. The membership of these committees is listed on http://www.kconfab.org/organisation/working_committees.html. Appeals can be reviewed by the independent Management Advisory Committee.

What does kConFab do?

kConFab ascertains families with multiple cases of breast cancer through the Familial Cancer Clinics. From these, kindreds useful for research purposes are chosen on the basis of the number of available affected and unaffected family members. These families are then offered the opportunity to participate in kConFab. If the families consent, additional family history, clinical, epidemiological and dietary information, and biological specimens are collected. These specimens include blood, pathology reports and fresh tumour and prophylactic material when available. Within a family, collection of samples may initially be limited to all individuals affected with breast or ovarian cancer (as well as carriers or obligate carriers of a known BRCA1 or BRCA2 mutation), all the first-degree relatives of these individuals (with both parents) and any additional family members in the direct ancestral line between affected individuals. Testing for BRCA1, BRCA2, ATM, p53, pTEN and PALB2 mutations is performed in as many of these families as possible in diagnostic laboratories in Australia or New Zealand with local funding as well as some support from kConFab.

How many families has kConFab collected?

Collection began late in 1997 and over 1700 breast cancer families have so far been recruited, each of which will have multiple affected cases or mutation carriers.

What biological resources will kConFab have available?

Family members participating in kConFab provide 20 mls of peripheral blood which is processed and stored at the Peter MacCallum Cancer Institute as Guthrie spots, plasma, lymphocytes for future transformation, non-lymphocytes for RNA isolation, and a white cell blood pellet for DNA isolation. In addition, confirmation of all cancers in these family members is sought from cancer registries, death certificates and pathology reports. Slides and blocks are not requested, nor paraffin sections cut, until needed by researchers and afterwards the block will be returned to the pathology laboratory. Some tissue microarrays are now available for research. Lastly, every opportunity is taken to obtain fresh tumours and normal breast and ovarian material from prophylactic surgery. This is divided into aliquots and sent frozen to the Peter MacCallum Cancer Centre for storage. For the past 3 years a rapid autopsy program has been run to collect metastatic tumour tissue. See <http://www.kconfab.org/progress/update.html> for kConFab's progress so far.

What information does kConFab hold?

Family history, clinical, treatment, epidemiological, pathological and mutation information are stored in a de-identified form on a central database designed and maintained at the Peter MacCallum Cancer Centre. The other kConFab data are available, in a de-identified manner, to researchers for approved research projects. Investigators using kConFab's material agree to submit new information found by that project to the central database so that molecular and biological information can be built up on these families and specimens.

How can kConFab be used for research?

kConFab is potentially a powerful tool to study the genetics, biology, epidemiology, pathology and clinical, psychosocial and other aspects of hereditary breast cancer. For example, it can be used to

- investigate the frequency, type, penetrance and phenotype of BRCA1 and BRCA2 mutations in the Australasian population
- determine the effect of modifier genes on the penetrance and phenotype of these BRCA1 and BRCA2 mutations
- identify more BRCA genes
- understand the relationship between environmental risk factors and genetic susceptibility
- examine the relationship between mutations in BRCA1/BRCA2 and prognostic indicators, pathological markers and clinical outcome
- study the molecular progression of breast and other cancers in mutation carriers
- study the psychological impact of testing and the effectiveness of genetic counselling in breast cancer families

When can an application to kConFab be made?

Applications can be sent to Heather Thorne (heather.thorne@petermac.org) at any time.

How does an application to kConFab for a research project get approved?

The steps involved in applying to kConFab for access to biospecimens (with accompanying data) are similar to those used in other large-scale epidemiological and genetic studies. In brief, they involve

- sending a brief letter of intent by e-mail to Heather Thorne (heather.thorne@petermac.org) at the Peter MacCallum Cancer Centre for circulation to the entire kConFab membership and
- submitting a research proposal, together with the usual ancillary material, to Heather Thorne at the Peter MacCallum Cancer Centre. Applications for biological material are reviewed by the relevant sub-committee(s). Final approval is then given by the Executive Committee. This application must be made within six months of submitting the letter of intent. If more than six months has elapsed, a new letter of intent must be submitted prior to the full application.

Details are provided in later sections of this document, and a flow chart of the process is available on <http://www.kconfab.org/access/AppProcess.html>.

If the proposal has not been approved by or submitted to a granting agency, kConFab may seek the opinion of external reviewers, whose reports will be reviewed by the relevant Sub-committees and then by the Executive Committee of kConFab. In the event of disagreement between the external reviewers and the various committee members, the final decision will rest with Professor Fox. In any event, final approval will be subject to appropriate ethical clearance. Appeals can be sent to the Management

Advisory Committee, whose membership is listed on http://www.kconfab.org/Organisation/Working_committees.shtml.

What about pilot projects?

Investigators may request permission to conduct a pilot project with the intent of establishing the rationale, feasibility or power of a full application. The results of a pilot study would not normally be expected to be publishable.

A pilot project involves limited numbers of specimens, in general:

- 30 germline DNAs
- 5 specimens of frozen tissue
- slides or DNA from <15 pathology blocks

However, the sample size will need to be sufficient to achieve the stated aims.

The same processes, application forms and decision criteria will be required for pilot and full applications, except that the need to full peer-review will be waived for pilot projects. Pilot projects will only be approved for one year. The decision to treat an application as a pilot or a full application will rest with kConFab.

How are amendments handled?

1. Amendments to the proposal originally approved by kConFab may be submitted at any time during the lifetime of the approved project. Review by the relevant sub-committee will be at the discretion of the chair, and, determination as to whether an amendment requires full review will be the responsibility of the relevant committee chair.
2. Amendments for minor changes in experimental procedures or small increases in the number of already approved samples and/or the amount of data supplied by kConFab will generally be approved automatically.
3. When the amounts of data and/or the types of samples requested in the amendment are significantly greater in quantity or different in kind from those originally approved, the amendment will be sent for review to the relevant kConFab Committee(s) and may be treated as a new proposal. Additional cost recovery charges will apply if it is considered a new proposal.
4. Generally, requests to add on a separate, previously established, external project to an approved kConFab project will be treated as a new proposal
5. When investigators/collaborators who were not included in the original proposal are named in the amendment, the project leader should provide the following information:
 - the role of the new person in the project
 - their location
 - what kConFab samples and data (including overall numbers), will be provided to them

The institutions to which the new investigators/collaborators are attached may be requested to sign kConFab's Materials Transfer Agreement.

Who should sign the kConFab MTA?

kConFab requires that an MTA be signed by any investigator who will receive a substantial amount of kConFab data or material.

Can additional investigators be added to approved kConFab projects?

Yes, the procedure in this case is that the PI of the project will request a signed MTA from any new collaborator to whom they wish to pass on material.

What are the responsibilities of investigators who use kConFab material?

The Chief Investigator(s) of the project agree:

- To sign the kConFab Material Transfer Agreement and not to distribute the material or data to investigators or institutions who are not named in the approved application.
- To list The Kathleen Cuninghams Consortium into Research on Familial Breast Cancer as an author on any resulting publications, in addition to any kConFab members who fulfill authorship criteria for the study as it progresses.

- To acknowledge the agencies that support kConFab's core activity in any resulting publications
- To submit an annual report on this project for the Executive meeting that occurs closest to the end of June each year. If an annual report is not submitted, the PIs will be blocked from receiving new biospecimens and/or data for any project until an annual report is submitted.
- To propose a timeline for monitoring the project
- To meet the costs involved in preparing and shipping biological specimens and in extracting data from the central database, if requested by kConFab.
- To notify kConFab of study completion. All studies will be deemed complete after three years unless re-application is lodged
- To lodge copies of relevant manuscripts utilizing the kConFab resource with kConFab
- To submit published data back to the Central Registry. In addition kConFab may request that unpublished data be sent to the Central Registry if no publication has been submitted in the 12 months following completion of the project.
- To return unused material to kConFab
- To obtain a signed MTA from any collaborator to whom they wish to pass on material for use in the approved project. This should be passed on to Heather Thorne with a request that kConFab consider the addition of the collaborator to the project.

How does kConFab attract new projects?

Information on the kConFab resource is available on the web site - <http://www.kconfab.org> - as well as a list of currently approved projects, and current letters of intent.

How will researchers know what is available?

Details of the kConFab resource are available from <http://www.kconfab.org/progress/update.html>. Alternatively Ms Heather Thorne (heather.thorne@petermac.org) or Ms Eveline Niedermayr (data manager; eveline.niedermayr@petermac.org) can be requested for more specific information.

How does kConFab protect the finite biospecimens resource?

Because biospecimens are a valuable and non-renewable resource (with the exception of lymphoblastoid cell lines) every effort should be made to extract the maximum amount of information from each specimen, and to avoid duplication of effort. For this reason the Biospecimens Sub-committee will encourage and facilitate cooperation and collaboration between potential competitors wherever possible. In the event that such cooperation cannot be achieved, the Sub-committee will report on the situation to Professor Fox for him to make a final decision. Resolution may involve identification of non-overlapping sample sets, or, if the projects are mutually exclusive, the rejection of a lower ranked application.

Because of the finite nature of this resource, kConFab is unlikely to ship large batches of biological material at one time, but instead will ask each applicant to suggest how the material may best be processed, including suggestions of batch sizes and milestones by which kConFab can monitor progress - for example, the publication or reporting of intermediate results.

How does kConFab assess the quality of biological or molecular information being submitted to the database?

Primary responsibility for the ethical and scientifically valid use of kConFab biospecimens and data rests with the Chief Investigators of the research projects. However, should problems arise, kConFab reserves the right, for the purposes of quality control, to initiate confirmatory analyses of materials previously released to researchers. In extreme cases kConFab may ask to review some raw data, and may institute some review before additional batches of material are given out. Discrepancies will be discussed with the investigator.

Procedures for Access to Biospecimens for Full and Pilot Projects (with accompanying data)

1. Before making an application for biospecimens (with accompanying data), researchers may wish to confer with Heather Thorne to discuss the rationale, feasibility and the appropriateness of the kConFab resource for the proposed study.
2. The applicant can download the Guidelines and Application Forms from the kConFab web site. At least two weeks before the application is submitted, the applicants must send a brief letter of intent (by email) to Heather Thorne at the Peter MacCallum Cancer Centre for circulation to the entire kConFab membership to allow the membership to comment on the proposed application.
3. Applications must be made on and according to the Application Forms, attaching relevant documents. Completed applications via email should be sent to Heather Thorne at the Peter MacCallum Cancer Centre. If the work to be done is funded by the National Breast Cancer Foundation (NBCF), also submit the funded NBCF grant research plan that details the biological samples and/or data to be used.
4. Full applications that have not had prior peer review may be sent by the sub-committees of kConFab to referees. If a proposal is currently under peer review by a granting agency, kConFab can provide a letter stating that the samples requested are available, subject to approval by the committees of kConFab once a full application has been submitted.
5. Applications and referees reports will be reviewed by the relevant sub-committee(s), which will assess whether the application comprises a scientifically justifiable, feasible, and high priority use of the biological material currently available. The applicant may be asked to respond to the reviewers' comments in writing. The sub-committee(s) may suggest some changes to the proposed application and will try to facilitate communication and collaboration between groups working on similar topics. In the event of trouble, the Sub-committees will do their best to find fair resolutions to conflicts between competing groups who simultaneously submit overlapping applications. Any member of the Sub-committees with a conflict of interest will be excluded from this assessment. Applications will also be reviewed by the Database Sub-committee so that they can suggest the mechanism and timescale for the delivery of the requested data, and also the costing if deemed necessary. Applications for data will be ranked in order of priority by the Chairpersons of the Executive and sub-committees.
6. The Sub-committees' recommendation will be reviewed by the Executive Committee at its next meeting or out of session by email and teleconference. Any member of the Executive Committee with a conflict of interest will be excluded from this review. The final decision will rest with Professor Fox as Principal Investigator of the kConFab grant. Professor Fox will then respond to the applicant in writing. Reasons will be given for refusal of all or part of the proposed use of material, and this may occur even if the grant proposal has approved funding. Conditions on, or restrictions of, use may be made. Appeals to decisions can be made to the independent kConFab Management Advisory Group.
7. Projects that require direct interaction with kConFab participants will always be referred to the Ethics Reference Group for comment.
8. Once the MTA has been signed by both parties, and ethical approval obtained, the project can proceed according to the agreed protocol.
9. Any significant deviations from the agreed protocol must be sent by the applicants in writing for approval before proceeding.
10. Samples will be shipped and data will be transferred to the kConFab database according to the agreed protocol.

11. Annual progress reports will be required by kConFab, to the Executive Meeting that occurs closest to June each year. Heather Thorne will notify all investigators when progress reports are due. Failure to submit an annual report will result in the blocking of all new biospecimens and/or data being supplied to the PIs until an annual report is lodged.
12. Data and biological material will be supplied as soon as possible after a request is approved. The onus is on the investigator to re-submit the application at a later date as the kConFab resource grows if additional material is required for the same project. Alternatively, if the original application was for 'all' of the specified material, then the onus is on the researcher to re-contact Heather Thorne regularly for additional material as it becomes available.
13. kConFab may charge the researcher for the preparation and shipping of biological materials.
14. kConFab reserves the right to withhold the supply of further material if the rate of progress is unacceptable.

APPLICATION FORM TO kConFab FOR WORK INVOLVING USE OF BIOLOGICAL MATERIAL

Title of Project: _____

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s): _____

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s): _____

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s): _____

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s): _____

Address of Principal Investigator: _____

Phone Number: _____ FAX: _____

e-mail: _____

We/I hereby seek permission from kConFab to undertake the research work detailed in the attached proposal according to the conditions specified kConFab. We/I will sign the kConFab Material Transfer Agreement and will not distribute the material or data to third parties. We/I will list The Kathleen Cuninghame Consortium into Research on Familial Breast Cancer as an author on any resulting publications, in addition to any kConFab members who fulfill authorship criteria for the study as it progresses. We/I will meet the costs involved in preparing and shipping biological specimens and in extracting data from the central database. We/I realise that there is the potential that this human biological material may contain infectious agents, and therefore should be handled appropriately. We/I will submit published data back to the Central Registry, or within 12 months of completion of the project, whichever is the sooner.

Signed: _____ Date: _____

Signed: _____ Date: _____

Signed: _____ Date: _____

* kConFab requires that an MTA be signed by any investigator who will receive a substantial amount of kConFab data or material.

CHECKLIST OF MATERIAL REQUIRED AS PART OF FULL AND PILOT APPLICATIONS FOR BIOSPECIMENS AND DATA

- Scientific proposal (up to six pages) including aims, hypotheses to be tested, significance, background, research plan with details of methods to be used and references. This should include the rationale for number and amount of samples requested, including considerations of statistical analysis and statistical power. Less than one page is required for a pilot project. If the work to be done is funded by the National Breast Cancer Foundation (NBCF), also submit the funded NBCF grant research plan that details the biological samples and/or data to be used.
- List of biological material requested including the type of sample, the number of samples, and the amount of sample.
- Completed kConFaB Data and Biospecimen Request Forms (see attached)
- Evidence of ethical clearance for the project including copies of approved institutional human research ethics applications and all correspondence with the human research ethics committee. Where applicable, this must be provided from each of the participating institutions.
- Evidence of approval for a grant application that has already undergone peer review by a funding agency. Wherever possible, kConFab would appreciate receiving copies of the referees' reports. This is not required for pilot projects.
- Names of three suitable referees for grants that have not already undergone peer review or for which peer review from an external granting body is not pending. Applicants may also nominate people whom they do not wish to review the application. This is not required for pilot projects.
- Information on the resources available to conduct the research (including source of funds, personnel, and maintenance).
- Publications of the Chief Investigator(s) for the last five years.
- Suggested timeline for the project including batch sizes and reasonable monitoring procedures for kConFab to use, and predicted time for submitting data to the kConFab database. Indicate when the first request for data and biological specimens will be made following approval of the project. Successive batches may not be shipped until data from the previous batch(es) have been received at the central database according to the agreed schedule. In the event that the data are incomplete or are otherwise unacceptable, kConFab reserves the right to withhold further shipments of material.
- Suggested protocol for shipping, including (a) mode of shipping, (b) address for shipping, and (c) suggested arrangement for payment of shipping.
- A outline of consulting agreements, collaborations and research projects between investigators named on the application and commercial organisations.

Procedures for applying to use data collected by kConFab (without biological specimens)

1. Before making an application, researchers may wish to confer with Dr Chenevix Trench to discuss the rationale, feasibility and the appropriateness of the kConFab resource for the proposed study.
2. Applications must be made on and according to the Application Form, attaching relevant documents. The application will include a Data Request Form for distribution to the Database Sub-committee so that they can suggest the mechanism and timescale for the delivery of the requested data, and the costing if appropriate. Completed applications should be sent to Heather Thorne at the Peter MacCallum Cancer Centre. Applications for data will be ranked in order of priority by the Chairpersons of the Executive, Family Review, Biospecimens, Pathology and Database Committees.

APPLICATION FORM TO kConFab FOR DATA (without biospecimens)

Title of Project:

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s):

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s):

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s):

Name of Applicant(s): _____

Role: _____

Should this person sign an MTA*? Yes _____ No _____ Don't know _____

Institution (s):

Address of Principal Investigator:

Phone Number: _____ FAX: _____

e-mail: _____

We/I hereby seek permission from kConFab to undertake the research work detailed in the attached proposal according to the conditions specified kConFab. We/I will sign the kConFab Material Transfer Agreement and will not distribute the data to third parties. We/I will list The Kathleen Cuninghams Consortium into Research on Familial Breast Cancer as an author on any resulting publications, in addition to any kConFab members who fulfill authorship criteria for the study as it progresses. We/I will meet the costs involved in preparing and shipping biological specimens and in extracting data from the central database. We/I realise that there is the potential that this human biological material may contain infectious agents, and therefore should be handled appropriately. We/I will submit published data back to the Central Registry, or within 12 months of completion of the project, whichever is the sooner.

Signed: _____ Date: _____

Signed: _____ Date: _____

Signed: _____ Date: _____

* kConFab requires that an MTA be signed by any investigator who will receive a substantial amount of kConFab data or material.

CHECKLIST OF MATERIAL REQUIRED FOR THE APPLICATION FOR kConFab DATA (without biospecimens)

- Scientific proposal (one to six pages) including aims, hypotheses to be tested, significance, background, research plan with details of methods to be used and references. This should include the rationale for the data requested, including considerations of statistical analysis and statistical power.
- Completed kConFab Data Request Form (see attached)
- Evidence of ethical clearance for the project including copies of approved institutional human research ethics applications and all correspondence with the human research ethics committee. Where applicable this must be provided from each of the participating institutions.
- Evidence of approval for a grant application that has already undergone peer review by a funding agency. Wherever possible, kConFab would appreciate receiving copies of the referees' reports.
- Names of three suitable referees for grants that have not already undergone peer review or for which peer review from an external granting body is not pending. Applicants may also nominate people whom they do not wish to review the application.
- Information on the resources available to conduct the research (including source of funds, personnel, and maintenance). If the work to be done is funded by the National Breast Cancer Foundation (NBCF), also submit the funded NBCF grant research plan that details the biological samples and/or data to be used.
- Publications of the Chief Investigator(s) for the last five years.
- Suggested timeline for the project including reasonable monitoring procedures for kConFab to use. Indicate when the first request for data will be made following approval of the project.
- An outline of consulting agreements, collaborations and research projects between investigators named on the application and commercial organisations.

CONTACT INFORMATION

Contact information for Heather Thorne at the Peter MacCallum Cancer Centre

heather.thorne@petermac.org

Telephone – 03 8559 6526

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eveline.niedermayr@petermac.org

Telephone – 03 8559 6529