Fernald Community Cohort

A Large Academic Biobank with a 20 Year Heritage

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U.S. Department of Energy
Uranium Processing Plant at Fernald Ohio

- Known as the Feed Materials Production Center (FMPC)
- Processed uranium ore and recycled materials to make highly refined uranium metal products used in DOE nuclear weapons production complex
- In operation from 1952 to 1989
Fernald Medical Monitoring Program (FMMP)

- The FMMP is the result of a class action lawsuit against National Lead of Ohio (NLO) and the U.S. Department of Energy (DOE) on behalf of people living near the Feed Materials Processing Center (FMPC) in Fernald, Ohio.

- The bases of the lawsuit were emotional distress and property value diminution.

- After a “summary jury trial”, the parties reached a settlement for $78 million. The settlement required that a medical monitoring program and epidemiological studies be implemented.

- Program was in operation, providing comprehensive medical screening examinations to 9782 program participants for 18 years (1990-2008).

- Data and biospecimens now are available to interested and approved researchers (over 50 studies).
<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Physician Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Medications</td>
<td>● Health history</td>
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<tr>
<td>● Family history</td>
<td>● Review of Systems</td>
</tr>
<tr>
<td>● Occupational, hobby, and environmental history</td>
<td>● Medications</td>
</tr>
<tr>
<td>● Detailed pregnancy and reproductive history</td>
<td>● Social history</td>
</tr>
<tr>
<td>● Oral contraceptive use history</td>
<td>● Comprehensive physical examination</td>
</tr>
<tr>
<td>● SF-36</td>
<td>● Blood and urine obtained at time of first exam and frozen for later use.</td>
</tr>
</tbody>
</table>
Fernald Medical Monitoring Program becomes the Fernald Community Cohort

- January 13, 2010. Agreement between the Fernald Citizens’ class and the University of Cincinnati transfers custodianship of the FMMP research resources to the University of Cincinnati.

- UC College of Medicine, Department of Environmental Health assumes responsibility for the Fernald Community Cohort.
Research Resources

What’s available in the Fernald Community Cohort database and biospecimen repository?
FMMP Participants
N=9782
Medical Condition Information

FMMP Physical examination

Outside medical records including:

- *Death certificates
- *Pathology reports
- Medical test reports
- Operative and discharge summaries.

- ‡ Exam findings coded with FMMP codes
- *Diagnoses coded with ICD-9 codes
- All information stored in a very large computer database.
Examinations: Whole Blood, Serum, Plasma and Urine Samples for future studies

At the first examination, three 1 ml aliquots of samples of various media were obtained.
- Serum
- Plasma
- Whole blood
- Urine
- Urine with buffer – to maintain pH at 7.5
- 15 aliquots per person- for future analyses

At later exams, serum and plasma were obtained on some participants.

In 2006-2008, additional whole blood and serum obtained on all participants who came for an exam.

Over 160,000 samples in five large freezers.
Value of the Archived Samples

- **Very large cohort:** Over 160,000 samples on over 9000 persons.

- **Prospective Cohort:**
  - Samples collected early in the Program, with many years of follow-up; can be used to identify genetic and proteomic predictors of disease.
  - Whole blood, serum and urine samples can be used to identify biomarkers of previous metal and chemical exposures prior to disease.
  - Very few resources of archived samples, with 15+ years of follow-up, exist.
Interval, in years, between blood sample collection and date of cancer diagnosis as of 6/2007

Frequency distribution for different intervals in years: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16.
Learnings: Biospecimen Storage

- Do not cluster all samples for a person in one freezer.
  - spread samples, by type, over multiple freezers

- Labeling practices change over time
  - use of a sample ID
  - bar coded labels
  - can’t re-label at minus 80°C.

- Alarm system and Co2 backup are essential

- Good freezer maintenance is essential (but expensive)
Learnings: Biospecimen Inventory

- Inventory database and queries: investment in design pays off
- Redundancy is good (binders and database)
- Keep up with software updates
- Periodic back-ups of computer inventory database.
- QC queries for duplicate records or no records
- Periodic freezer inventories, especially after samples have been moved because of freezer maintenance issues
Data screen record for one sample
Queries and Reports

REPORTS/QUERIES

Choose Report
Info for Specific UCID and Sample

Continue
Close

Specify UCID: 60100
Select Sample Type: Plasma

Report
Query

Preview
Close
# FMMP Specimens used per UC ID

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Freezer</th>
<th>Shelf</th>
<th>Tray</th>
<th>Slot</th>
<th>Old Box #</th>
<th>New Box #</th>
<th>Drawn</th>
<th>Project Code</th>
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<tr>
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<td>2</td>
<td>3</td>
<td>60</td>
<td>9,2</td>
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<td>FAS</td>
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<td></td>
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<tr>
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<td>1</td>
<td>144</td>
<td>6,2</td>
<td>159</td>
<td>FD</td>
<td>1991</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma</td>
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<td>1</td>
<td>144</td>
<td>6,3</td>
<td>159</td>
<td>FD</td>
<td>1991</td>
<td>COL09</td>
<td>10/7/2009</td>
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<tr>
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<td>3</td>
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<td>9,7</td>
<td>1879</td>
<td>FAR</td>
<td>1994</td>
<td>COL09</td>
<td>10/7/2009</td>
</tr>
<tr>
<td>Plasma</td>
<td>7</td>
<td>2</td>
<td>11</td>
<td>9,5</td>
<td>158</td>
<td>FC</td>
<td>1991</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Learning:
Consent requirements change over time

- In 1990 consent requirements were minimal.
- Be proactive about keeping your IRB informed.

FERNALD MEDICAL MONITORING PROGRAM
CONSENT TO PARTICIPATE

The Fernald Medical Monitoring Program is designed to provide you a free, comprehensive evaluation of your current health and risks for future disease. The program is entirely voluntary. We hope that you will take advantage of all the examinations and tests offered you. However, you are free to refuse any part or all of the program, the procedures we will follow, the type of information you will receive, potential risks of the testing, and the measures we have taken to preserve confidentiality.
4) **Laboratory Tests** - Blood and urine samples will be obtained for a series of screening tests which will include blood counts, blood salts, liver and kidney function tests, a blood sugar, and an urinalysis. Two samples of blood will be obtained and frozen for future additional testing if necessary. Your blood will **not** be tested for HIV antibodies (AIDS test).

separately. No one is to have access to any of this information except as authorized by the Fernald Settlement Fund Trustees. If authorized by the Settlement Fund Trustees, scientific data or medical information may be analyzed and presented in court, at scientific meetings, or in professional journals so that the overall results of this Program may be useful to others. However, no presentation or report shall include your name or any other identifying information which might compromise your right to privacy; and every reasonable effort shall be made to ensure your anonymity.
Consent in 2007 and thereafter

7. Blood and urine samples for research - You are asked to take part in a component of the Fernald Medical Monitoring Program that includes collection of blood and urine samples for use in future research studies. Researchers will use blood and urine samples in conjunction with personal information in FMMP records to study how different components of blood and urine might be related to disease and how genes, lifestyle, and our environment may lead to disease. We will ask you to donate 3 tubes of blood (about 4-6 teaspoons) that will be drawn from a vein in your arm at the same time as we are taking blood for the usual tests that are part of the FMMP examination. We also ask that you allow us to freeze a portion of your urine sample.

VI. RESEARCH

Research Using Data

If authorized by the Fernald Settlement Fund Trustees, scientific data or medical information may be analyzed and presented in court, at scientific meetings, or in professional journals so that the overall results of this Program may be useful to others. However, no presentation of results will include your name or any other identifying information, which might compromise your right to privacy; every reasonable effort shall be made to ensure your anonymity.
Under federal law, researchers who use information about the health of their research participants are required, except in specific circumstances, to get written permission to use their participants’ health information for the research study. We are asking for your authorization to allow researchers approved by the Fernald Settlement Fund Trustees to use or disclose certain information about your health. Your information may be used for research studies currently being conducted (attached) or future research studies approved by the Fernald Settlement Fund Trustees.
Research Using Blood Samples

Your samples will only be released for research purposes to researchers who have been approved by the Fernald Settlement Fund Trustees.

The exact tests that will be performed in future research studies are not known at this time but are likely to include the following: 1) the study of blood proteins; 2) the study of genes and changes in genes that may be involved in hereditary and non-hereditary disease development; and 3) the study of how race/ethnicity, age, lifestyle, the environment, and other factors may play a role in disease development. At no time will your name and address, or any other identifying information, be given for research purposes without your permission. Instead, requests for use of the information in the study will be handled in the following way.

Researchers who are interested in using blood samples have to complete a research plan with specific information about their study, including a description of how they will use the information. Plans will be reviewed by a group of experienced scientists and the Fernald Trustee, who will judge each plan for its scientific merit, its potential contribution to the prevention or cure of disease, and for the qualifications of the research team. Because we realize that the information and samples you provide are an invaluable contribution to science, their use in any research study will be carefully weighed. If a plan is approved, your information and samples will only be shared by us with an approved researcher after your name and address, and any other identifying information, have been removed and a code number has been given.

If an approved researcher would like to collect more information and/or blood samples, not routinely collected by the research staff, we will contact you to explain the study, and you will have the choice of whether to participate before you would be contacted directly by the researcher.

By signing this consent form you agree to give to the FMMP all rights to the access and control of any obtained blood, urine or tissue. The FMMP may retain, preserve, or dispose of these samples and may use them in future research studies for an unlimited period of time. The results of future studies conducted may be published or presented to scientific groups, but you will not be identified by name in these publications.
Access to Data and Biospecimens

- Any qualified researcher may apply to use the data and biospecimens for research. Application is online at FMMP website.

- Applications for access to the data and biospecimens are reviewed and approved by an Advisory Committee. Data are de-identified before being sent to researchers.

- Over 50 studies have been approved, conducted by researchers from UC, the National Cancer Institute, and the University of South Carolina. Currently UC is collaborating with the University of Vermont on developing a large study of biomarkers and early effects of exposure to radiation.

- 46 publications in scientific journals have resulted from these studies.
PROCEDURES FOR AUTHORIZING ACCESS TO THE FERNALD COMMUNITY COHORT (FERNALD MEDICAL MONITORING PROGRAM) DATABASE AND ARCHIVED BIO-SAMPLES

Research Director: Susan M. Pinney, PhD  susan.pinney@uc.edu
Program Coordinator: Jeannette Buckholz, MSN, buchnojm@ucamill.uc.edu

(The Fernald Community Cohort refers to the medical records, computerized data, and biospecimens of the Fernald Medical Monitoring Program.)

1. Access to the Database or Archived Samples for Purposes of Analysis

a.) Only individuals and groups specifically approved by the Fernald Community Cohort-s (FCC) Advisory Committee will be permitted access to the FCC database or archived samples (frozen whole blood, serum, plasma and urine).

b.) Any individual or group who wishes access to the FCC database or archived samples for purposes of analysis will submit an application to the FCC-Research Resources Director. who, in turn, will obtain the decision of the FCC Advisory Committee. If the application requests data only (no biosamples requested) the Committee may meet by telephone conference to review the application and make a recommendation. Applications that request biosamples must be reviewed and voted upon at an in-person Committee meeting.

The completed application will include the individual’s name, title and affiliations, qualifications, categories of interest in the FCC data or archived specimens, disclosure of any affiliations with persons, agencies, companies, or attorneys with an interest in the Fernald project or related projects/litigation. The application must contain a focused research question or hypothesis statement, and all of the requests for data or biosamples must relate directly to the research question or hypothesis statement. The completed application also will include a list of specific items in the database to which he/she needs access AND/OR a description of the number and types of archived samples requested. Applications requesting access to archived samples also must include a sample size calculation or statement of the number of samples needed with accompanying rationale. Applications also must include a copy of the updated NIH biosketch or curriculum vita of each investigator.

1.) Each application for access to the database will include a confidentiality statement signed by the applicant that includes assurances that no one other than the approved person or persons will be permitted to have access to downloaded information. In addition, applicants must agree to return the downloaded data to the FCC-Research Resources program within the UC Department of Environmental Health for storage at the conclusion of their analyses or at the end of their approved access to the database. If an approved researcher wishes to retain data until a manuscript has been accepted, he/she may petition the Research Director with that request. In all cases, information/data must be returned when authorization for use expires.
Fernald Community Cohort Advisory Committee

- Eula Bingham, PhD
- Jeanette Buckholz, RN, MSN
- Lisa Crawford
- Ranjan Deka, PhD
- Paul DeMarco, Esq
- James Heubi, PhD
- Shuk-Mei Ho, PhD

- Kathleen Lang, MD
- Vince Martin, MD
- Graham Mitchell
- Susan Pinney, PhD
- Carol Schroer
- Sue Verkamp
- Gary Volz
- Robert Wones, MD
- Edwa Yocum
Fernald Community Cohort Advisory Committee
FERNALD MEDICAL MONITORING PROGRAM (FMMP)
APPLICATION FOR ACCESS TO THE FMMP DATABASE OR ARCHIVED SAMPLES

STUDY TITLE:
1. Application Date: Approval Date:
2. Applicant’s Name:
   Principal Investigator: YES NO
   Project Name (if different from study title):
3. Address:
4. Phone Number:
   Email address:
5. Title(s):
6. Institutional Affiliation(s):
7. Do you have any affiliation with persons/agencies including but not limited to the DOE, DOD, and CDC, companies, or attorneys with an interest in the Fernald Medical Monitoring Program or Fernald Settlement Fund or related projects/litigation?
   ____ No
   ____ Yes
   If yes, please explain in detail any such affiliations (attach additional pages if necessary).
Learnings:
Periodic quality assessment of samples are an important component of quality assurance

- Determine long term stability of specimens for future analyses
- Determine DNA quantity and quality for future analyses
- Determine future needs and resources for specimen preservation
- Test the specimen locator system
2000 – Quality Assessment

- Randomly sampled 80 serum samples from four freezers.
- 20 specimens chosen from each freezer
- An additional 50 specimens of whole blood were selected for DNA evaluation

- Samples thawed; chemistry and protein analyses performed by Alliance Laboratory.

- Results compared with those obtained on the same sample at the time the sample was drawn (first examination)
Integrity of cryopreserved samples is excellent!

- **2000 quality assessment**
  - Lyophilization (freeze dry) effect found to be 7%, 7%, 4% and minimal
  - Enzyme degradation – none in AST and ALT
  - DNA good quantity and quality; only 2 samples had minimal DNA

- **2005 quality assessment**
  - 1 ml whole blood yielded 10-20 ug DNA
  - DNA fragments of 15kb and greater
  - Frozen serum compared to fresh serum in proteomic studies, and did not show degradation; protein identification was consistent
Sample Selection: Randomly sampled 10 whole blood and 10 serum samples from four freezers.

Protein Analysis: Dr. Detlef Schumann at the UC Genomics Research Institute tested 10 serum samples for proteomic studies, comparing sample to fresh standard human serum purchased from Sigma. None of the samples showed significant protein degradation.

- Concentrations were in the expected range for serum
- 2D gel patterns are consistent with what would be expected
- Protein identification by mass spectrometry of the same 4 spots from 3 different samples; consistently identified the same proteins.
2005 and 2006 Quality Assurance

- **2005 DNA Evaluation:** Dr. Marshall Anderson at the UC Genomics Research Institute evaluated the quality and quantity of DNA in 10 whole blood samples, by agarose gel electrophoresis and spectrometry.
- All samples had sufficient DNA for re-sequencing, polymorphism/mutation, and/or comparative genomic (CGH) analyses.

- **2006 Methylation Studies:** Dr. Shuk-mei Ho used 16 whole blood samples, from 1991-1993, for DNA methylation studies.
- “The quality of DNA is great, intact up to 15Kb and longer.”
Thank you.
<table>
<thead>
<tr>
<th>Incident Cancer (since enrolling in FMMP)</th>
<th>920</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td>107</td>
</tr>
<tr>
<td>Breast Cancer (including in situ)</td>
<td>193</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>179</td>
</tr>
<tr>
<td>Melanoma</td>
<td>91</td>
</tr>
<tr>
<td>Urinary</td>
<td>77</td>
</tr>
<tr>
<td>Leukemia</td>
<td>21</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>38</td>
</tr>
</tbody>
</table>
8. Are you requesting (please check one or both options):

___ Downloaded data file from the FMMP database

___ Archived biospecimens

Describe the research questions and/or hypotheses for which you intend to use the FMMP data or archived samples (attach additional pages if necessary). The research question or hypothesis should be focused with well-defined dependent and independent variables. Please identify the study design (case-control, cross-sectional, prospective, intervention, etc.)

9a. Are you requesting a data file?
If you are requesting a data file, please identify the categories of data in the FMMP Database that you would require to perform your analyses. If you have examined the FMMP database data dictionary, you may use a separate page to list the specific variables (and the file source of the variable).

Please circle: Specify type of data in each category:

NO YES Demographic Data:

NO YES Questionnaire Data (specify):

NO YES History and Physical Exam Data (specify):

NO YES Lab Data (specify):

NO YES Other Test Data (specify):
9b. Are you requesting archived samples?  YES  NO

If you are requesting archived samples, specify the number and types of samples you require for your study. Additionally, present your eligibility requirements and sample size calculations or other documentation of the need for the quantity of samples you are requesting. If you are not requesting samples, write in a "0" for each type of sample.

| Whole blood | Number of samples requested |
| Plasma      |                            |
| Serum       |                            |
| Urine – not buffered |                      |
| Urine - buffered |                         |

What are the eligibility requirements for the participants providing these samples (such as sex, age at sample collection, presence or absence of certain diagnoses, etc.)?

What data do you need about the participants providing the samples? (Please include these data request in your response to question 9a and also sign the data agreement in addition to the sample agreement.)

Please provide sample size calculations or other documentation of the need for the quantity of samples you have requested. (You may attach this explanation and documentation.)

10. IRB Institution: University of Cincinnati Medical IRB

   Study IRB Number: Approval Expires on:

   Please attach a copy of your latest IRB approval memo.

11. Describe how your proposed analyses will benefit the FMMP participants or the public at large.
AGREEMENT FOR USE OF THE FMMP DATABASE

STUDY TITLE:

1. I attest that I have no personal interest in the Fernald Settlement Fund, related projects, or related litigation other than what is listed on my application. I further attest that I have no affiliations with individuals, attorneys, or companies who have an interest in the FMMP or related litigation other than those listed on my application.

2. I agree to maintain strict confidentiality of the data I receive from the Fernald Program.

3. I agree that no one other than persons named in the application(s) and myself be permitted to have access to data from the Fernald Medical Monitoring Program.

4. I agree to return the original Fernald data and any copies of the original data to the Trustees for storage at the conclusion of the analyses or at the end of my approved interval of access.

5. I understand that the FMMP and the Fernald Settlement Fund are not responsible for costs incurred in downloading and analyzing the data.

6. I agree to conduct only those analyses that are outlined in my application.

7. I agree to submit a brief annual progress report to Dr. Robert Wones.

8. I agree to provide a copy of any abstract, manuscript or presentation, reporting results of analyses of the FMMP database or archived samples, to the Trustee or his designee for review prior to submission to a conference or professional journal and prior to any other publication or dissemination. Under most circumstances, the Trustee will respond within five (5) business days.

9. I agree to conduct my analyses in such a way that the identity of individuals, if known, will remain confidential.

10. I agree that all manuscripts of results from my analysis will be written so that no identification of individuals is possible. I will acknowledge the Fernald Medical Monitoring Program as the source of the data for my analyses.

Signature: ____________________________

Print name: __________________________

Date: ____________________________
AGREEMENT FOR USE OF THE FMMP ARCHIVED SAMPLES

STUDY TITLE:

1. I attest that I have no personal interest in the Fernald Settlement Fund, related projects, or related litigation other than what is listed on my application. I further attest that I have no affiliations with individuals, attorneys, or companies who have an interest in the FMMP or related litigation other than those listed on my application.

2. I agree to maintain strict confidentiality of individual information (including genotypes) that I acquire from specimens received from the Fernald Program.

3. I agree that no one other than persons named in the application(s) and myself, and staff who work directly under our supervision, will be permitted to have access to the samples from the Fernald Medical Monitoring Program.

4. Upon the conclusion of the study described in this application, I agree to either dispose of biospecimen samples remaining after my analyses and any materials derived from those samples or to amend my application to the Fernald Trustee for use of the samples another study. If I wish to retain any remaining sample materials from the sample, or amplified DNA from the sample for additional research, I agree to first petition the Trustee with that request and obtain the Trustee’s approval before conducting any additional analyses.

5. I understand that the FMMP and the Fernald Settlement Fund are not responsible for costs incurred in preparation or analysis of samples.

6. I agree to conduct only those analyses that are outlined in my application.

7. I agree to submit a brief annual progress report to Dr. Robert Wones.

8. I agree to provide a copy of any abstract, manuscript or presentation, reporting results of analyses of the FMMP database or archived samples, to the Trustee or his designee for review prior to submission to a conference or professional journal and prior to any other publication or dissemination. Under most circumstances, the Trustee will respond within five (5) business days.

9. I agree to conduct my analyses in such a way that the identity of individuals, if known, will remain confidential.

10. I agree that all manuscripts of results from my analysis will be written so that no identification of individuals is possible. I will acknowledge the Fernald Medical Monitoring Program as the source of the biospecimens used in my research, and the source of the corresponding data.

Signature: ________________________________

Print Name: ________________________________

Date: ________________________________