



Genetic Research Studies in CALGB: Ethical, Social, and Policy Issues

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Background: What Do We Mean by “Genetic”?

- Traditionally the term GENETIC: having an inherited component-maternal or paternal origin, passed down through generations
- Currently the terms GENETIC/GENOMIC: of or having to do with DNA or DNA products (RNA, mRNA, mtRNA, proteins, etc)
- Majority of diseases are not familial; however every disease has a genetic (DNA) component
 - ~90% of breast cancer is sporadic
 - ~10% of breast cancer is inherited
 - ~50-80% of inherited breast cancer is associated with mutations in BrCa 1 or 2 genes
 - Therefore, only 5-8% all breast cancer is explained by BRCA1/2

Somatic versus Germline DNA Studies

- Somatic genetic studies: evaluate acquired changes in the TUMOR tissue (*mostly tumor DNA, but also tumor RNA*)
 - Frozen tumor tissue
 - FFPE tumor tissue
 - Tumor cells in fluids (*pleural effusion, ascites, sputum*)
- Germline studies: evaluate changes that are inherited, passed down from one generation to the next in the “germ” cells (*ovary, testes*)
 - DNA and RNA pattern in every nucleated cell of the body
 - Whole blood (*PBLs*), buccal swabs, other normal tissue.

CALGB Genetic Research

- 1994: CALGB was the first cooperative group to initiate a germline DNA research study
- CALGB 9484, Dr. Ross McIntyre: collect and extract DNA from breast cancer patients enrolled in CALGB breast studies for BRCA1 and future studies
 - DOD funded study, restrictions in informed consent
- IRBs had significant concerns regarding risks to participants:
 - 5/37 main member institutions activated study
 - Only 250 specimens obtained
- Manuscript described challenges of performing genetic research in a cooperative group setting

Examples of CALGB Cancer Genetic Research Studies: 12 years Later

- Family cancer studies (tumor and germline DNA): Sibling study in colon cancer for inherited susceptibility (*CALGB study, Monica Bertagnoli, GI Committee*)
- RNA Expression studies (tumor RNA): classification of breast cancer based on RNA expression: basal versus luminal cell tumors; triple negative phenotype (*Chuck Perou, Breast Committee*)
- Cancer Control/Epidemiologic studies (germline DNA): Leiden Factor V and risk of blood clots in breast cancer patients receiving tamoxifen (*Judy Garber, Cancer Control*)
- Pharmacogenetic Clinical trials (germline DNA): Predicting response to drug therapy by evaluating small variations (polymorphisms) in cancer patient's DNA to "personalize" or "individualize" therapy (*Howard McLeod, PET committee*)

What is different about genetic research compared to other types of medical research?

Germline DNA Research - Using Normal DNA Inherited from Parent to Child


- Prediction of future disease or behavior in addition to diagnosis of current problem
- Research can involve currently unaffected individuals as well as affected individuals
- Implications beyond individual - other family members; others sharing a common ancestral origin
 - Groups of people in communities
 - Identified by ethnicity, geographic location, ancestry

Benefits of genetic research

- Medical interventions for diseases with treatments
- Registry for future medical interventions: prevention, diagnosis, treatment for you and your family for diseases with no current treatment options
- Autonomy: right to know/right not to know
- Life planning:
 - Reproductive decisions
 - Lifestyle changes
 - Health insurance , disability insurance
 - Life insurance

Risks of Participating in Genetic Research

- Violation of privacy
 - Access to confidential or sensitive information by third parties
- Stigmatization, psychosocial issues
 - Anxiety, depression, identity issues
- Potential for family discord
 - Non-paternity revealed, disagreement related to participating in studies
- Uncertainty of eventual development (or severity) of disease in currently unaffected individuals
 - Prophylactic oophorectomy (*removal of ovaries*) to prevent ovarian cancer
- Misuse of genetic information
 - Discrimination in insurance, employment, services (*education, credit*)



IN THE FURRY PAGES, ALL GOOD THINGS OR ANYWAY THINGS COME TO AN END. AS IT USUALLY HAPPENS, SHE WRAPS UP HER CRIMINAL BELIEFS... AND THESE BEARS MOOSE OUT OF THE EAST — THOUGH NOT BEFORE PROVIDING A GRAPHIC DEMO

The New York Times Magazine
MAY 14, 2006 \$5.00

Body-Stuff Politics
Those blood and tissue samples you routinely give — where are they? Who owns them? What are they being used for? And how come you don't know? *By Rebecca Skloot*

Also: Strawberry Shortcake on Florida for Justice

Body Stuff Politics:
Those blood and tissue samples you routinely give—where are they? Who owns them? What are they being used for? And how come you don't know?

*NYT. April 16, 2006.
Rebecca Skloot*

Major Ethical and Policy Issues

1. Respect for autonomy of research subject
(*integrity and dignity*)
2. Protection from breaches of confidentiality;
privacy concerns (*security*)
3. Professional concerns, including intellectual
property concerns/financial benefit/sharing data
(*transfer*)

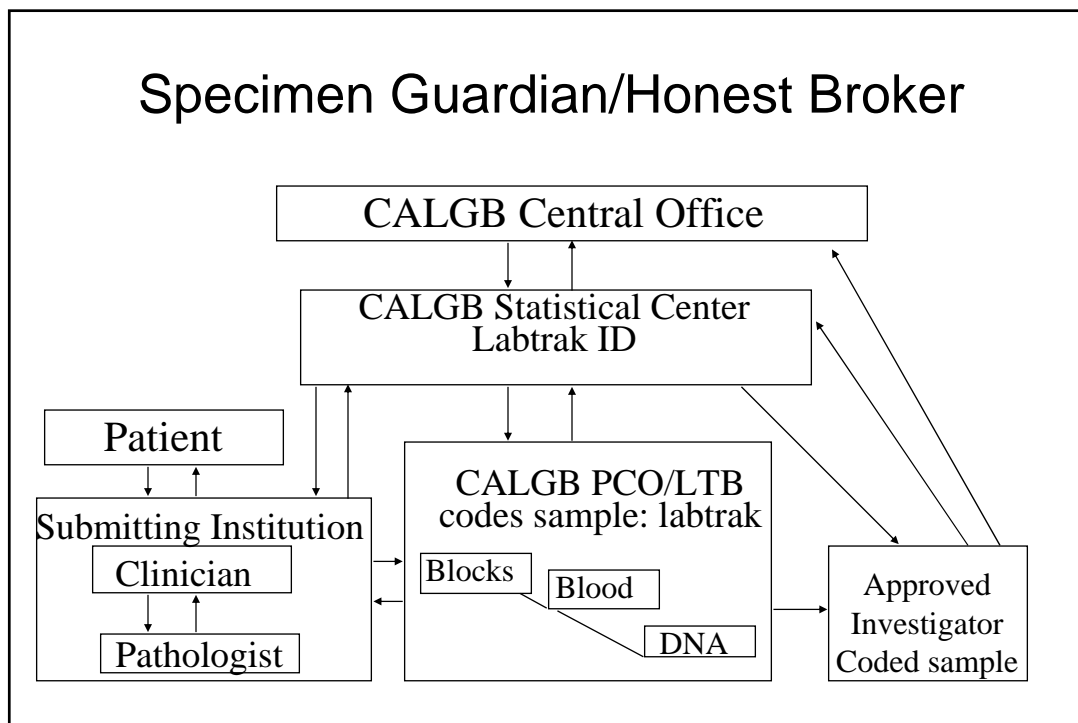
Important Issues

- What are the barriers to and implications of participation in cancer genetic research?
- How can we (CALGB) protect patient privacy and maintain information confidential, both clinical and results of research?
- Will the individual/family have access to information (*aggregate or individual*) obtained from their sample?
- Is there a plan to address conditions that would compel disclosure?
- What happens if the individual wants to terminate further participation in the project?

How Does CALGB Currently Address These Issues?

1. Implementation of honest broker model to protect privacy and maintain confidentiality
2. Implementation of specific policies for germline DNA studies
 - Informed consent for all prospective studies
 - Investigator agreements regarding use and sharing DNA
3. Interaction with other experts, advocacy groups to develop improved policies and practices

Specimen Guardian/Honest Broker



Specimens

- All specimens sent first to CALGB PCO or LTB
- Specimens will then be sent to researchers as per protocol schema
- No specimens will be sent to any investigator until the CALGB Central Office receives documentation of IRB approval from investigator's institution
- No specimen use (*assays, markers*) unless indicated in approved protocol*

**New assays, investigators, methods change require amendment/new concept*

Specimens

- Research labs must use the CALGB Web Application LabTrak to receive and monitor specimens
- All leftover specimens (*DNA, RNA, slides, frozen specimens, fluids, etc*) must be returned to CALGB central repository
- Patients can terminate participation in a study at any time
 - PCO or repository will destroy remaining DNA (*or return block to submitting hospital*). However DNA already used/distributed to a researcher and resulting data cannot be retrieved.

Repository Safeguards to Protect Patient Privacy, Confidentiality, and Medical-Legal Concerns

- Researchers are blinded to the identity of the specimen
- Specimens are identified with a unique identification number (Labtrak ID) generated by the CALGB Web Application LabTrak.
- Specimens are not distributed with any patient identifying information

Linking of Codes and Data by CALGB Statistical Center Only

- Information from repository, results of research studies, patient treatment response, and other clinical information are stored separately at CALGB Statistical Center.
- Strict security and limited access to link specimen and research information at CALGB Statistical Center.
 - Only select personnel at Statistical Center (*not Study Chair or other research investigators*) will have ability to match unique id number with identity of patient and with other coded clinical information or coded research results.

Documents Required at Central Office Prior to Study Activation and Specimen Distribution

1. Approval letters from EC and disease or modality committee(s) (e.g. LLCS, Breast, GI, GU, Respiratory, Pathology, PET)
2. IRB approval letter from all investigator's institutions (*wherever work will be conducted; not just from study chair*)
3. HIPAA privacy authorization from investigator's institution if needed
4. Letter of investigator agreement (*gen'l P and P*)
5. Letter of banking agreement (*if relevant*)
6. Contractual agreement with industry (*if relevant*)
7. Letter of germline agreement (*if relevant*)
8. Conflict of Interest Form(s)
9. Registration of lab with CALGB LabTrak and Central Office
10. CTEP approval (*if study uses 100 or more specimens*)

Investigator Agreements

- All data submitted in appropriate format to CALGB Statistical Center for analysis.
- Investigator will be blinded to clinical information and identity of specimen.
- All publications (*abstracts/ms*) are first reviewed and approved by CALGB office prior to submission (*authorship/time schedule*).
- No disclosure of information to patient, physician, third party, etc; no clinical decision-making based on STCS research results (*unless specified in protocol , e.g. eligibility/randomization*).

Investigator Agreements

- No secondary or future use of specimens (*DNA, RNA, protein, sections, etc.*) without Working Group and Executive Committee approval – requires new concept and/or amendment to protocol.
- No sharing or banking of specimens for future use; all specimens are returned to PCO or other CALGB resource after assays complete
- If specimens or DNA, RNA, proteins are processed, stored in course of study, they are under guardianship of CALGB. Appropriate policies and procedures apply.

Investigator Agreements

- Any changes to investigators, objectives, assays, or significant methodology changes requires approved amendment/new concept*.
- Studies that involve DNA obtained from normal cells/tissue must follow CALGB DNA policy-patient consent, banking policy, no disclosure of information; certificate of confidentiality, etc.

**see your protocol editor*

Germline DNA Studies: CALGB STCS Policies

- Informed consent for studies of inherited genes must be obtained prospectively, use CALGB consent form*
- Currently, participants are asked to grant broad permission for using specimens in subsequent germ-line studies (*including polymorphisms*); using honest broker system to protect privacy, confidentiality, minimize risk
- Heritable studies in CALGB are limited to cancer
- Non-disclosure of information policy

*CALGB-wide template under revision

Disclosure of Information in CALGB Germline DNA Studies

- Results from CALGB heritable studies, as most other investigational studies, are not disclosed to the patient/participant, their family, or their physician or any other third party.
- If disclosure is specifically approved and indicated in the protocol (e.g. *eligibility or randomization*), the conditions for disclosure must comply with CALGB and local IRB policy and other relevant regulations
 - CLIA approved lab, pre and post test counseling,etc

CALGB Policies Governing Germline DNA Studies

- Banked specimens not originally intended for germline studies, may be used for studies of heritable genes, but require reconsent* of the participant/family
- A Certificate of Confidentiality (DHHS) should be obtained for each study to reduce risk of forced disclosure of genetic information and minimize risk to study participants (*see CALGB Administrator*).

**depending on nature of study, may meet conditions for waiver*

What Areas Still Need Addressing? What Efforts are Underway in CALGB?

- Use of uniform consent form throughout all CALGB studies: CARE, PET, CS
- Standards for blood handling, DNA extraction and storage: PCO, GBC, ISBER
- Policy for data sharing especially for sequence data and pharmacogenetic studies: CO, CS, NCI
- Disclosure of research results: conditions and process that would compel disclosure: CARE, CS, NHGRI, NCI

Resources

- Thank You! Please contact us with any suggestions for improvements or questions!
- Lynn.dressler@case.edu
- www.calgb.org

