Position Paper on the Testing of DNA and Tissue in Human Research.

Edison Liu, M.D.
Executive Director
Genome Institute of Singapore
gisliue@nus.edu.sg

November 8, 2001

With Assistance by Stella Tan

Executive Summary

Singapore wishes to establish the ethical and legal parameters on tissue and DNA research to guide its biomedical research initiative. A critical element in formalizing the trust in tissue-based research is the role of the Institutional Review Board (IRB), and the transparency of the regulatory system. In this position paper, I have proposed a number of solutions that may assist Singapore achieve its goals in the biomedical sciences and propel this country as a leader in the arena of the ethical and social issues of tissue and DNA based research.

1. The Common Pact:
The study of human tissues should be viewed as necessary for citizen health, but the research community must also commit to the notion that their research must have as its goal to improve human health and not simply to satisfy theoretical curiosity.

2. The distinguishing boundaries:
Without this exercise, rules could be promulgated that are either too broad to be interpretable, or too narrow to be useful. In tissue and DNA research, several boundaries define the need for different regulations:

- Therapeutic vs. observational uses of research tissues
- Whole organs vs. tissue fragments
- Germline DNA vs. Somatic DNA
- The study of genes with high penetrance phenotypes vs. those with low attributable risk
- The impact of the test results: community vs. individual risks

3. The regulatory issues:

IRB review for tissue and DNA research is essential for ethical conduct of research. Informed consent, which is the act of informing the subject of the experiment and asking their consent in participating in the study, is deemed appropriate when research may have adverse outcomes to the subjects. There are mechanisms (establishment of a formal data escrow system' case-based precedents that help guide local IRBs in their decision-making and formalizing the concept of a central or national IRB for the conduct of national studies) that will allow for quality research to be conducted with waivers for informed consent and without the need for anonymization, which limits the utility of clinical material.

I propose that clear guidelines be developed for the use of previously consented patient materials by defining the requirements for reconsent. Inherent in this proposal is my belief that reconsent is unnecessary in many situations as the data escrow systems can be an alternative to provide the confidentiality necessary to permit the issuance of a waiver for reconsents.

I propose that research on somatic changes, or involving genes associated with limited hereditable phenotypes be exempt from obtaining reconsent. Those that specifically target germline mutations with obvious and adverse phenotypes should obtain informed consent/reconsent. The local IRBs *with national guidance* are suited to make these distinctions.

There is no specific right to ownership of tissues for the patient once the tissue has been separated from the body and after permission has been given through a clear informed consent process. The institutions funding and collecting the tissues are the owners and has ethical responsibilities with this ownership.

4. Proposals for the governance of Singapore's tissue and DNA research:

I propose the following platforms for confidentiality: *data escrow and honest broker/agent*. The data escrow structure is that an impartial third party, that is not the researcher, keeps the tissue/DNA "identifier key". I believe that Singapore is unique suited to initiate one of the first public domain data escrow platforms and become a world leader in this technology. I believe that the data escrow system coupled with key mediators whom I call honest brokers (akin to data safety and monitoring board members), can establish a coded link between a tissue block repository to disease registry tracking data.

Singapore is highly compact and has a history of social consensus and hence I propose the establishment of a *National IRB* specifically formed to review proposals of comprehensive national scale (many sites) and those employing the linked disease registries, which are national resources. The decisions of this national IRB would be accepted as the overriding decision throughout the country.

A major concern is the forced disclosure of this information by insurance companies, employers, or the government. The key issue is the protection of individuals from loss of job, and loss of medical/health insurance because of genetic tests either performed for clinical care, or in the course of research. I believe that there are several legislative options for Singapore that can balance the protection of citizen privacy: laws to protect insurability and certificates of confidentiality.

Lastly, I propose to further clarify the requirements for informed consent and reconsent with the following extended guidelines:

- The informed consent and reconsent are required when therapeutic interventions, physically accessing new tissues for research, or new information gathering requiring direct patient contact are considered.
- Informed consent and reconsent are required if the research on archived samples seeks to test germline mutations in highly penetrant phenotypes, and to link these results to clinical data and patient identifiers.
- Informed consent and reconsent/IRB review are not required when samples are anonymized.
- Informed consent and reconsent can be waived: (a) If the patient will not be recontacted and if the test does not involve interrogation of germline DNA mutations associated with highly penetrant phenotypes. (b) If the linkage between the patient identifier and the test outcome can be sufficiently obscured by electronic means and the use of Data Escrow agents. This guideline specifically permits the use of coded information without informed consent or reconsents since the primary investigator will not have access to unique identifiers of each patient. It is therefore important for the Singapore BAC to clearly define the acceptable parameters for such a Data Escrow interface.

Consent, confidentiality, and IRB oversight are the cornerstones of ethical regulation in tissue and DNA research. My major criticisms of the recent US system governing tissue and DNA research have been that the regulations do not recognize the differences between the varying forms of tissue/DNA based research and that there have been no definitive structural mechanisms within the IRB system that seeks to resolve overarching conflicts and controversies. Singapore, through the current BAC process, has the opportunity to establish a regulatory framework that not only protects research subjects, but also facilitates scientific discovery.

Introduction

The use and the study of human tissues have been the hallmark of medical research since the days of Hippocrates. Dissection of human cadavers for anatomical education was followed by post-mortem examinations as a major tool for the medical observational science. The discipline of histopathology, now considered standard of medical care, was, in fact, an experimental science that led to the 1906 Nobel prizes of Ramon y Cajal and Golgi. Thus, the extension into molecular and genetic technologies for the study of human tissues is in line with a long and tested history of medical research.

Along with this history of advances have also been controversies when research and social customs/religious standards clash. The center of this controversy has been the issue of respect for human remains, which is often interpreted as respect for cultural customs. Dissection of cadavers has been either prohibited or severely limited, and anti-vivisection laws enacted in response to the perceived disrespect during the scientific analysis on human remains. More recently, these issue resurfaced, first with the reaction of families in Ireland upon disclosure that the remains of infants were used for educational purposes, and second with the desire of native Americans to re-inter the skeletal remains of ancestors that have been put on display as archeological finds.

Currently, the issues have been further complicated by the ability of DNA studies to divine the future risk of an individual and his or her relatives to disease. Thus, access to one person's tissue could be interpreted as knowledge of the medical destiny of an entire family. Balancing these concerns, however, is the power of genetic technologies to deliver precise diagnostics, and in identifying the constitutional predisposition to disease. This knowledge will lead to tailored preventative and therapeutic interventions that inevitably will improve a nation's health.

Singapore wishes to establish the ethical and legal parameters on tissue and DNA research to guide its biomedical research initiative. The discussion herein is commissioned by the BAC subcommittee on Human Genetic Testing and will be restricted to comments on the analysis of human tissues including DNA in clinical translational and epidemiological research. I will not be touching on the harvesting of human tissues for the purpose of therapeutics. Because of time constraints, I will not be able to detail the history of the controversies surrounding this topic with significant documentation. Though I hope to be informative in my discussion, I will concentrate on my observations from the perspective of a translational and population scientist, and as a former government official with the National Institutes of Health (USA) involved in governing tissue and DNA based research. From these observations of the critical problems, I will propose a number of solutions that may assist Singapore achieve its goals in the biomedical sciences and propel this country as a leader in the arena of the ethical and social issues of tissue and DNA based research. Much of the supporting information has been provided by my long-time colleague, Lynn Dressler from the University of North Carolina at Chapel Hill through her thesis work in the ethics of tissue and DNA research. This information

is seen in various attachments to this document. I have also appended in Attachment VI comments on this proposal by colleagues in the field so that the BAC can see other opinions as well.

1. The Common Pact

The fundamental ethics for human tissue research are embodied in the Belmont principles: respect for persons, beneficence, and justice. It is also appropriate to extend this discussion for clinical/epidemiological research on human tissues to include three more basic premises:

1.1 Clinical and epidemiological research is *essential for public health*
1.2 Clinical and epidemiological research must be *done for the public good*
1.3 Clinical and epidemiological research must be *performed in an ethical fashion* conforming to the cultural consensus of the population.

The study of human tissues should be viewed as necessary for citizen health, but the research community must also commit to the notion that their research must have as its goal to improve human health and not simply to satisfy theoretical curiosity. This pact between the scientific community and society is the necessary balance that will ensure that only science with impact will be conducted and for society to be reassured that only the best and the most ethical science will be permitted. It is this inherent trust between investigator and the constituent population that builds the permissive environment for tissue-based research. These fundamentals will be important in framing the downstream discussion and the resultant regulations. A critical element in formalizing this trust is the role of the Institutional Review Board (IRB), and the transparency of the regulatory system. A well constituted, and well-funded IRB can provide the imprimatur of community consensus needed in the ethical validation of the research.

This is an unusual time in the history of biomedical sciences. Technology has dramatically accelerated the rate of discovery such that leads pertinent to treating and curing human disease emerge more quickly than the capacity to validate them. The limiting factor is now access to highly annotated tissues from well-structured studies. An important issue to resolve is the reuse of tissues collected from historical studies. The maturity of these investigations allows for linkage to disease and to clinical outcomes without waiting for events to occur which often takes years to decades. Current regulations in the US are unclear about the reuse of these tissue banks. Resolution and clarity will greatly facilitate scientific investigations.

2. Defining the Problem: What are the distinguishing boundaries?

In constructing regulations, it is important to identify the problems these rules are created to solve and the conceptual boundaries they govern. Without this exercise, rules could be promulgated that are either too broad to be interpretable, or too narrow to be useful. In tissue and DNA research, several boundaries define the need for different regulations:

- Therapeutic vs. observational uses of research tissues
- Whole organs vs. tissue fragments
- Germline DNA vs. Somatic DNA
- The study of genes with high penetrance phenotypes vs. those with low attributable risk
- The impact of the test results: community vs. individual risks

2.1 *Therapeutic vs. observational uses of research tissue*

The collection of tissues for processing to derive therapeutic agents requires a significant level of sophistication to following Good Laboratory Practice (GLP) guidelines. Thus, there is unanimity that such tissues (lymphocytes, organs, etc.) should be procured with informed consent and with IRB review. There is also consensus that tissues obtained for the purpose of

research require IRB approval (e.g., buccal swabs, blood samples). The controversy, however, lies in the analysis of unconsented tissues, primarily tissue blocks or archived tumors, obtained during the course of standard care. Previously, pathologists might perform a study on paraffin-preserved tissues for marker validation without IRB approval and without informed consent. Over the years, the emerging standard in the US is for informed consent to be obtained for these samples unless the tissue blocks are anonymized prior to study. It is implicit that IRB review is needed prior to use of these tissues. Though IRB review is considered reasonable, the need for informed consent is thought to be problematic by many in the scientific field since the cost and time needed to conduct this research becomes prohibitive (impracticable) despite the significant value of this information. Resolution for this problem of consent and reconsent will greatly facilitate clinical and epidemiological research.

2.2 Whole organs vs. tissue fragments

Perception of respect is important in the use of tissues for research. Thus research on tissue fragments has different cultural connotations from research on whole organs, or on whole fetuses. Whole organs and organisms (entire cadavers and fetuses) are thought by many cultures to be spiritually closer to the intact human. However, the focus of this paper is on tissue fragments and important points to be resolved are whether IRB approval is necessary for some forms of tissue research and when informed consent is required. We believe that when dealing with whole organs, entire cadavers, or whole fetuses, IRB approval and informed consent should be required. In this manner community standards will be weighed against scientific importance in a transparent manner.

A separate category of tissue work involves the use of tissues and organs/cadavers for educational purposes. It is my position that educational uses should be governed by the same regulatory standards but with provisions for institutional/departmental approvals. For example, it is unnecessary to require a proposal to be tendered for every course in pathology or histopathology each semester. Instead, consideration should be given for yearly “bundled” approvals for the use of cadavers for anatomy courses, or for tissues in a group of histopathology courses. In all cases strict confidentiality by preventing patient disclosure is required.

2.3 Germline vs. Somatic DNA

Not all DNA research is the same and therefore DNA research should not be regulated in a monolithic manner. The greatest distinction is between the analysis of DNA from germline as compared to DNA from somatic sources. Germline mutations are the genetic defects that are passed on from generation to generation. Somatic mutations are, however, lesions that exist only in the end organ (such as liver), which may then give rise to a cancer. These somatic mutations are restricted to the local tissue and cannot be passed on to other generations. Germline DNA analysis, such as from normal tissues for the purpose of studying hereditable conditions has the potential impact not only on predicting the future health of the subject but also the condition of his/her relatives. Mutations in BRCA1 associated with susceptibility to breast and ovarian cancer are examples of germline aberrations with such impact. Somatic DNA/tissue analysis from tumor specimens examines the genetic changes in the tumor that occur during the conversion to cancer. Amplification of HER-2/neu in breast cancers is an example of somatic genetic alteration affecting the behaviour of the tumor but is not inherited. This information does not have hereditable implications and therefore is limited to the patient and her condition.

The College of American Pathologists (CAP) grappled with this question of whether genetic information is different from other medical information and determined three characteristics that have been proposed to account for that difference: power, predictiveness, and implications for individuals other than the patient (Grizzle et al. Arch Pathol Lab Med. 123:296-300. 1999, see Attachment I). A qualitative difference between genetic and non-

genetic data is that genetic data may provide information about more than just the individual from whom the data are derived. The CAP group cited that "potential differences in the extent of harm that may result from the misuse of different kinds of medical information and thus there is a need for an operative definition of genetic information." They suggest that genetic tests should be defined as tests that provide information used for diagnosing an inherited disorder acknowledging the difference between somatic changes and germline mutations.

It is our position that whereas germline DNA research requires IRB approval and informed consent in all cases, somatic DNA/tissue research should be performed with IRB approval but may be conducted with a waiver of informed consent even when linked to patient information.

2.4 *Study of high penetrance genes vs. those with low or no attributable risk*

In the study of germline DNA, the ability of the analysis in predicting future risk of disease in the subject is highly variable. In the case of Huntington's disease, the identification of a germline mutation provides near certainty that the disease will manifest, and that there is risk to family members. By contrast, the information from sequencing for single nucleotide polymorphism (SNP) discovery has no immediate predictive value and therefore no risk to the patient and his family members. In all cases involving germline DNA analysis, the general principle remains that IRB approval and informed consent should be obtained unless the samples are anonymized. When studying gene mutations with definitive risk of disease, provisions should be made for GLP certified genetic testing and counseling. When the research is to define the risk associated with a mutation, and the genetic tests used have not been "hardened" to GLP quality, clinical testing can be made available to subjects after the results of the study have been announced in the aggregate. These approaches are now becoming standard operating procedures.

One controversy, however, is whether such a stringent approach is necessary for all germline genetic research. For example, functional polymorphisms of drug metabolism genes have little to no significance in normal human biology except when an individual is challenged with specific drugs. The metabolism may be altered depending on the genetic configuration of the individual, but the medical consequences are limited. In this situation, the germline analysis has less implication for health and for social issues such as insurability than that of a highly penetrant phenotype such as in BRCA1 or Huntington's disease gene mutations. Therefore the requirements for the conduct of studies involving BRCA1 gene mutations and those of drug metabolism genes may be different and still be ethical.

The second controversy is in the need for reconsent for studies not included in the original informed consent. The issue is whether new research can be performed on tissues for questions not originally consented. For example, germline DNA is obtained from a case control study of SNP associations with lung cancer. The original informed consent specifically explains this study goal. Three years later, a putative gene for lung cancer has been identified but the association needs to be validated. The DNA from this case control study is ideal to perform the validation study. Should all patients in the SNP study be contacted and reconsented for approval to test the new lung cancer gene? Currently, reconsent is often (but not uniformly) required by local IRBs, but there are no definitive guidelines for when the requirement for reconsent can be waived. The importance of resolving this reconsent issue is that cohort and case control studies are difficult and costly to mount. If a new study were required for all new markers, the cost would make this research impracticable. Reconsent is similarly impracticable if each new marker required recontacting the patients for consent.

We believe that there should creative and ethical alternatives to requiring reconsent in many retesting situations. For example, the establishment of data escrow structures may permit the delinking of clinical data to patient identifiers to preserve confidentiality.

2.5 *The impact of the test results: community vs. individual risks*

Some in the U.S. have advocated the principle of community consent. The basis is that if a germline mutation is focal to a specific ethnic population, then research on individuals, even if informed consent was obtained, may adversely affect the ethnic population in terms of discrimination. Thus, if a study is directed at ethnic groups, then some form of group consent may be needed. We believe this is a dangerous concept because it violates the right of the individual subject to define the communities to which he/she belongs. Moreover, questions such as what constitutes a community and who speaks for the community will always remain unclear. While U.S. regulations require that IRB members represent the diversity of the community be sensitive to local factors including cultural backgrounds and community attitudes, there is no regulation requiring group or community consent. We therefore recommend that the concept of community consent be rejected.

3. ***Defining the Problem: What are the regulatory issues?***

Major issues relating to DNA and tissue based research involve informed consent, the need for IRB approval, and confidentiality. The critical questions that need to be addressed are:

- When is IRB approval required?
- When is informed consent necessary? What is the definition of practicable?
- Can research be performed on tissues for questions not originally consented?
- What should the guidelines be for tissues collected in the course of standard medical care?
- Should subjects be given a portion of profits from the research? Should the investigator be allowed to benefit from this access to critical tissues?
- In registries where consent is implicit and part of public health, how linked can the data be?

With any solution, several factors must be considered: rules must be clear and simple in principle; rules must be communicated to the research and clinical community; and there should be set times to reevaluate and even reconstruct the rules so that regulations governing human research remain dynamic and responsive to both scientific and social needs.

3.1 *When is IRB approval required?*

IRB review is the fundamental community check on human investigation. However, the operational activity of the IRB can either improve or hinder research. A bureaucracy that is not guided by principles, not dynamically changing, and that is risk adverse will hinder progress. Thus, it is important for Singapore to establish a system that, from the beginning, embraces best practices. We believe that IRB review for tissue and DNA research is essential for ethical conduct of research. Such a review can be by the complete IRB panel or through a single designated official in cases when a waiver of consent is acceptable. We also believe that there should be different forms of review tailored to the impact of the research on patient confidentiality, patient risk, and the advancement of science. We believe that it is unreasonable to ask that each IRB arrive at local standards for every case especially in a country that is compact and whose systems are central and integrated. The recent experience in the field of research ethics in western countries, especially in the U.S., can help frame the discussion for Singapore (see Attachment II definition of a human subject). However, there are problems and constraints of the U.S. system engendered by its diverse cultural society, its focus on individual rights, and its legalistic/litigious approaches that Singapore can rationally bypass. It is our goal to recommend regulations involving tissue and DNA research that will place Singapore in the forefront of the interface between science, public health, and ethics. Thus, we believe that IRB review (even to obtain a waiver of informed consent) should be obtained for all forms of tissue and DNA research, but that the rules need to be clear, and the procedures tailored to optimize public good.

3.2 When is informed consent necessary? What is the definition of practicable?
Informed consent is the process of informing the subject of the experiment (risks, benefits, alternatives) and asking their voluntary consent to participate in the study. Informed consent is deemed appropriate when research may have adverse outcomes to the subjects. In therapeutic investigations where an intervention is given, there is an absolute requirement for informed consent. This is because all therapeutic interventions have potential adverse outcomes. In observational studies, such as epidemiological and clinical investigations looking at linking a biomarker to the incidence or severity of disease, the impact of the results may be far-reaching, such as those involved in germline mutations in highly penetrant disease genes, or have minimal impact, such as associations with low attributable risk. Again, in all cases, whenever an intervention is needed to obtain tissues for research purposes alone (such as blood), informed consent is necessary.

However, the controversy resides in two situations: first, when research is performed on tissues obtained through standard clinical care, and second, when experiments are performed on DNA or tissues which were not covered in the original informed consent document. In large clinical and epidemiological studies, rigid adherence to obtaining informed consent in the use of archived samples may make important studies so costly as to render the research impracticable. Much of the controversy has been in the definition of impracticable, and the threshold for providing a waiver of informed consent. This has been compounded by the diversity of opinions of local IRBs in the requirements for informed consent and reconsent, and the unwillingness of the US federal government to providing strong guidelines in this arena.

The Office for Protection from Research Risks (OPPR) (or OHRP – Office for Human Protection changed in the year 2000) in the U.S. federal government opines that a waiver of consent can be obtained if the IRB finds: “1) the research involves no more than minimal risk; 2) the waiver or alteration will not adversely affect the rights of the subject; 3) the research could not practicably be carried out without the waiver or alteration, and 4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.” (from OPRR, 1993 referring to 45 CFR 46). The 1993 guidelines do stress the IRB carefully consider if the study truly qualifies as minimal risk. However, there are no guidelines as to what constitutes minimal risk or what is considered impracticable. The absence of guidelines and a formal mechanism to vet consensus on these definitions has been a major problem.

The National Bioethics Advisory Commission (NBAC) of the United States grappled with this question of waiver of consent in their 2001 report (http://bioethics.gov/pubs.html). Implicit is that IRB oversight (either by the entire committee or by the IRB official) is needed: “When a study if of minimal risk, informed consent is no longer needed by a subject as a form of self protection against harms. However, it is still appropriate to seek consent to show respect for the subject unless it is impracticable to do so. Thus when important research poses little or no risk to subjects whose consent would be difficult or impossible to obtain, it is appropriate to waive the consent requirement.”

NBAC recommends that IRBs should operate on the same presumption that research on coded samples is of minimal risk to human subjects if:
a) the study adequately protects the confidentiality of the personally identifiable information obtained in the course of research
b) the study does not involve the inappropriate release of information to third parties and
c) the study design incorporates an appropriate plan for whether and how to reveal findings to the sources or their physicians should the findings merit such disclosure (i.e., disclosure guidelines).

In determining whether a waiver of consent would adversely affect subject's rights and welfare, NBAC recommends that IRBs consider:

a) whether the waiver would violate any state or federal statute or customary practice regarding entitlement to privacy or confidentiality
b) whether the study will examine traits, commonly considered to have political, cultural, or economic significance to study subjects (such a inherited traits research to affect employment, health insurance, social stigmatization)
c) whether the study's results might adversely affect the welfare of the subject's community.

NBAC suggests that coded samples be treated the same way as identified tissues, which means that those studies with coded samples still require IRB review, but may not require informed consent (waiver of consent) if the research does not present more than minimal risk to the subject.

Current U.S. federal regulations indicate that whenever appropriate the subjects of waived consent will be provided with additional pertinent information after participation (45 CFR46.116(d)(4). In general, NBAC felt this fourth consideration of waiver of consent is not relevant to research using human subjects and may be harmful if it forced investigators to recontact individuals who may not have been aware that their tissue was used in research.

We believe that there are mechanisms that will allow for quality research to be conducted with waivers for informed consent and without the need for anonymization, which limits the utility of clinical material. The mechanisms that will be discussed include:

a) The establishment of a formal data escrow system
b) Case-based precedents that help guide local IRBs in their decision making and in developing national consensus
c) Formalizing the concept of a central or national IRB for the conduct of national studies.

3.3 *Can research be performed on tissues for questions not originally consented?*

A major piece in the informed consent discussion has been the issue of reconsent. Recently, many epidemiological or clinical studies have assembled tissue and DNA samples for its primary analysis. As the clinical data matures, possible associations with patient outcome render the collected tissues highly effective in answering medically relevant questions. This is especially true when new putative markers of disease are uncovered and the validity of the associations can be tested on these archived tissues. For example, breast cancer samples have been collected for a study on HER-2 amplification and prognosis. Three years later, a putative gene for drug resistance has been identified and a polymorphism in this gene is associated with greater resistance to adjuvant chemotherapy but this association needs to be validated. The DNA from the tumor blocks from this clinical study is ideal to perform the validation study. Will it be necessary to contact the patients and obtain informed consent for every new marker tested on the original samples?

In the past, these archived tissues were considered the property of the investigators and therefore the concept of obtaining consent for the testing of new and emerging markers was considered unnecessary. However, the specter of germline DNA testing with its downstream implications for insurability and family health raised the level of concern, but the regulatory standards remain unclear. We propose that clear guidelines be developed for the use of previously consented patient materials by defining the requirements for reconsent. Inherent in this proposal is our belief that reconsent is unnecessary in many situations. We also believe that data escrow systems can be an alternative to provide the confidentiality necessary to permit the issuance of a waiver for reconsent even in linked situations. Lastly, we suggest that laws be promulgated that will protect the family histories and genetic test results obtained in research situations from being used to deny insurability or in criminal proceedings. This

means that no other governmental or private agency can access the tissues and the research data unless permission is given. Such laws will be necessary to ensure the public that the government supports population-based research as a tool to achieve public health.

3.4 *What should the guidelines be for tissues collected in the course of standard medical care*?

Over the years, it has become implicit that IRB approval (either reviewed by the committee or by a responsible official) is needed prior to use of tissues even in those collected during the course of standard clinical care. Most commonly, a waiver of informed consent permitted the investigator to explore association studies without the onus of seeking and recontacting the individuals. The emerging standard in some US IRBs, however, is for informed consent to be obtained for these samples unless the tissue blocks are anonymized prior to study. Cited for this shift has been the fear that germline information can be obtained that might disclose knowledge of hereditable conditions. Many scientific groups have resisted this move to require informed consent on archived clinical material arguing that the risk to the patient is small, the benefits to society great, and the cost and time needed to access this consent is prohibitive (impracticable). Indeed, the collective information in standard pathology tissue archives will support the development of many markers of human disease at remarkably low cost and with short timelines.

We believe that the problems have been in the confusion between germline and somatic research, and the notion of penetrance/attributable risk (see above). If a clear and acceptable demarcation can be made between disclosure risk and the need for informed consent/reconsent, these problems can be resolved. Thus, we propose that research on somatic changes, or involving genes associated with limited hereditable phenotypes be exempt from obtaining reconsent. Those that specifically target germline mutations with obvious and adverse phenotypes should obtain informed consent/reconsent. The local IRBs *with national guidance* are suited to make these distinctions. Alternatives to obtaining informed consent would be to anonymize the tissue and its associated clinical data. To limit the ability to identify specific patients in a population by “triangulation” of clinical parameters, the use of data escrow agents may be needed. These conditions can be decided by an informed IRB.

The level of clinical information collected for such studies has also been scrutinized. Review of medical records has been the preferred analytical approach. Such research requires IRB approval, but informed consent/ reconsent should be waived once the investigator can provide assurances to the IRB of provisions for patient confidentiality. The need for informed consent comes when recontact is needed for accession of more clinical data. We propose that patient recontact be a demarcating principle for the need for consent/reconsent.

Central to the regulations governing points 3.3-3.4 is the definition and concept of patient confidentiality. Again, the problem in implementing the regulations has been the conflict between the theoretical vs. operational definitions. Some ethicists claim that any exposure of information even in protected archives can be considered a potential breach of confidentiality and require informed consent/reconsent. The College of American Pathologists (CAP) outlined important operational recommendations (Grizzle et al. Arch Pathol Lab Med. 123:296-300. 1999): CAP contends that “confidentiality means that information will not be disseminated freely” implying a fiduciary duty not to disclose the information to others without the person’s consent, actual or implied, or otherwise in his or her interest.” They recommend that pathology departments develop written procedures concerning privacy and confidentiality protections, including procedures for releasing information for research. Like OPRR (now OHRP), they recommend that data be coded and stored physically separate from clinical or personally identifying information. Security policy and procedures should be written out. They consider, however, once these safeguards are firmly in place that provisions for waivers of

consent could be given.

Similar to NBAC, the CAP paper suggests that "when information about the specimen sources is withheld from researchers and any link is provided only through *IRB approved confidentiality procedures*, the risk to research subjects from unauthorized breach of confidentiality is minimal." Again, this puts burden of responsibility on the IRBs to have criteria for approval of mechanisms of security and appropriate processes of unlinking data. Unfortunately, there has been no governmental leadership on this topic and the ensuing ambiguity has caused problems.

One important concept brought forward by the CAP paper is that research data should not be considered genetic information. "It is important to realize that information developed in the course of research generally is not valid patient information for use in genetic counseling. Therefore research data should not be considered genetic information as that information is used in statutory information." This is a significant point in the discussion of what needs to be disclosed to patients/subjects of their individual data after research is completed.

3.5 *Should subjects be given a portion of profits from discoveries*? *Should the investigator be allowed to benefit from this access to critical tissues*?

The central issue of this question is who owns these tissues. We believe that there is no specific right to ownership of tissues once the tissue has been separated from the body and after permission has been given through a clear informed consent process. This has been the principle governing organ and blood donations and functions well. Patients may demand, and researchers may decide to share the downstream profits from this tissue access, but it should not be a requirement for any tissue accession programme. Since no individual investigator actually privately supports his/her own tissue collections, it also means that the investigator is not the owner. Instead, the institutions funding and collecting the tissues are the owners, holding ethical responsibilities with this ownership.

The direct sale of clinical material to a commercial entity is a larger societal issue. Patients will support biomedical research, but should not be expected to support the sale of their tissues without some remuneration (as a one-time payment) or prior consent where they waive remuneration. Waiver of remuneration is commonly done in organ donation and can be a model for tissue accession for research. In this model, a society determines that the donation of organs for transplantation is sufficiently important for the public good that all organ donations are managed publicly and funded by non-profit/governmental sources. The donors ask for no remuneration, the recipients do not pay for the organ, but the doctors and the hospital performing the transplantation receive compensation for their services. The same conceptual paradigm can be applied for tissue-based research. The donation of tissue for research is for the public good (both for public health and public prosperity) and those individuals and institutions working on this tissue may benefit from this research because the ultimate outcome is better medical products for patients, and more economic activity for the country. This model works if there the Common Pact as described in section 1 is accepted. The perception should be that this research is not solely for academic gain, but for the public good. This also requires that governmental or non-profit agencies be involved in assuring that the best science is done, and that specific ethical guidelines are followed.

Recently, in the US, there have been voices suggesting that patient donors should be provided royalties from the use of their tissues. The assignment of downstream intellectual property (IP) rights and licensing agreements to the tissue donor is impracticable and unenforceable. Even more dangerously, such a system may encourage individuals to "sell" their tissues to the highest bidder, thus establishing an untenable ethical situation. Therefore, such allowances should not be entertained.

3.6 In disease registries where consent is implicit and part of a public health programme, how linked can the data be and how should it be used in research?

The governance of national disease registries deserves special attention, because of the mandatory nature of the information collection and the ubiquity of the coverage. The information from these registries is vital in monitoring the public health of a country and for public policy. In addition, disease registry data is often the foundation of impact epidemiological research. This has been borne out by the fact that much of the best public health research is performed in those countries with advanced and enforced disease registries and accompanying infrastructure: the US, Scandinavia, China.

Singapore is quickly developing a world-class disease registry system that can be used for public good through biomedical research. The development of effective and ethical but streamlined approval processes for national registry research will make Singapore a unique international center for population studies. One concern voiced frequently related to the IRB approval process for disease registry research is the number of IRB approvals that are necessary to initiate a study. The original intent of local IRB control is that local sensibilities may be better voiced in this format. For epidemiological studies with limited sites, and for countries with large geographical space and cultural diversity, this local overview is important. For Singapore, with its compactness and history of centralization, epidemiological studies using this national resource studying questions of broad national importance may not require the same local scrutiny. Streamlined approval processes for such comprehensive studies serve to advance public health knowledge in a manner unique in the world.

We therefore propose the establishment of a National IRB specifically formed to review proposals of comprehensive national scale especially using the linked disease registries. This national IRB may initially reside in the BAC and evolve as needs arise. The composition and intention of this National IRB is to have the expertise to review the social and health implications of such global public health research and to ensure that patient confidentiality is secure. The decision of this National IRB will be accepted by all other IRBs if there is no comment after a one month study period. If, within the month of receipt of the National IRB decision, the local IRB finds an aspect objectionable, it can opt-out of the national study. We propose that this system be given two years trial, at the end of which, a more formal system can be enacted.

4. ***Proposals for the governance of Singapore's tissue and DNA research***

4.1 Principles:

We propose that the governance of tissue and DNA research in Singapore be driven primarily by principle and not solely by process. For this reason, the acceptance of the Common Pact in a form outlined in section one is important. This pact declares that tissue and DNA research is essential for public health and implicitly states that the regulatory system should facilitate this research but always in an ethically rigorous manner. It begins with the individual centric focus of western thought and adds the communal good as part of the equation.

Some of the recommendations below extend outside the boundaries of operational doctrines espoused by some thought leaders in the U.S. concerning DNA repositories and research. A summary of these current concepts is noted in Attachments II and III, which is excerpted from notes by Dr. Lynn Dressler (University of North Carolina, Chapel Hill). Attachment IV has the draft recommendations from European Society of Human Genetics (ESHG).

4.2 *Platforms for confidentiality: Constructing a dynamic regulatory organization to advance the common good*

Data Escrow: The concept of data escrow arises from the desire to separate the investigator from the primary source of patient information so as to limit the potential for inadvertent

disclosure of confidential information. This is especially useful in situations where research tests are proposed that are beyond what was originally consented. The structure is that an impartial third party that is not the researcher keeps the tissue/DNA "identifier key." Investigators can access clinical data and link it with their molecular findings only by coded means through this third party. Access is determined by a predefined governance process. This set-up is especially important in research situations where rich clinical information is linked to a well-structured tissue or DNA repositories. For example, when a new molecular test is employed that was not available or even conceived during the writing of the original informed consent document. To avoid the intrusion and the cost of recontact and reconsent, new tests can be validated in this coded/limited access approach still maintaining patient confidentiality. This is especially important in cohort studies where survival and disease outcomes are part of longitudinal follow-up of patients. The ability to test associations of clinical outcome with emerging candidate markers is of great importance and can only be practicably done if recontact/reconsent of patients for each new marker is waived. A major genomics company, Genomics Collaborative Incorporated (GCI) uses this structure as its fundamental principle in organizing their tissue and data collections (see outline in Attachment V). Their third party agent is:

Recall Information Management
2109 Bering Drive
San Jose CA. 95131
Tel 408 453 2753
Fax 408 441 6826

With advanced computer security, such data escrow systems can provide reasonable assurance for a high level of security. The key requirements for an Data Escrow Agent is that he/she has no stake in the research, there is a clear and transparent governance system in place, the computer systems are sufficiently advanced, and there are provisions for the data should the support company falter. As concerns for personal data security grow, there will be a market niche for data escrow platforms not only in the health care sector, but also in financial information as well. We believe that Singapore is uniquely suited to initiate one of the first public domain data escrow platforms and become a world leader in this technology.

Honest broker/honest agent: Consent, confidentiality, and IRB oversight are the cornerstones of ethical regulation in tissue and DNA research. IRB has jurisdiction over research regardless of whether informed consent is required. However, there are situations where archived data or tissues of great scientific value are available for research but consent was not obtained at the time. There are a large number of paraffin tissue banks coming from standard pathology laboratories that potentially represent a rich substrate for validation and discovery. The unique potential for this resource in Singapore is the ability to link with survival and disease registry databases that would augment the scientific value of these tissues. Here, reconsent would render the advantage null because of the cost of recontact and the perceived intrusion by individuals/family members during this recontact process. The dynamic tension is between the primary researcher and the regulatory IRB and surrounds the question of whether patient confidentiality can be maintained. We believe that the data escrow system coupled with key mediators whom I call honest brokers (akin to data safety and monitoring board members), can establish a coded link between a tissue block repository to disease registry tracking data. This code can be held by the data escrow agent, the tissue held by the investigative unit/repository, and the survival/registry data residing at the Ministry of Health (MOH) sites. The linkage takes place at the data escrow agency so that neither the MOH nor the investigator has all the data/identifiers. This process is overseen by the honest broker.

4.3 *National IRBs*

The rationale and proposed operation of a National IRB is described in section 3.6. We propose the establishment of a national IRB specifically formed to review proposals of

comprehensive national scale (many sites) and those employing the linked disease registries, which are national resources. The purpose is to reduce the time and expense of reviewing a national population based study by all participating local IRBs. This is justifiable in the Singaporean situation since the country is highly compact and has a history of social consensus thus making it likely that a single national IRB would discharge their duties appropriately. The specific use of disease registry data in a linked fashion to tissues and other databases should trigger the use of this national IRB. The decision of this National IRB will be accepted by all other IRBs if there is no comment after a one month study period. If, within the month of receipt of the National IRB decision, the local IRB finds the study objectionable, it can opt-out of the national study, but it cannot amend. This National IRB should be restricted to reviewing those studies of comprehensive national scale and using MOH or other governmental databases. It probably should not be used as an appeals court for the decisions of the lower IRBs.

4.4 *Legislative solutions*

The crux of the confidentiality problem is the potential loss of rights and of personal assets if genetic information is disclosed. A major concern is the forced disclosure of this information by insurance companies, employers, or the government. The key issue is the protection of individuals from loss of job, and loss of medical/health insurance because of genetic tests either performed for clinical care or in the course of research. In the US, laws protecting genetic "rights" of an individual are usually rather porous (with "loop holes") and selective (directed against only one or a small number of diseases) rather than comprehensive. For example, some states in the US have laws specifically preventing the discrimination based on sickle cell diagnosis but not any other genetic diagnosis. In the absence of legislative relief from the possible loss of job or insurability, laws have been established that limit access to genetic information. We believe that there are several legislative options for Singapore that can balance the protection of citizen privacy, with that of the need to advance public health. We propose several that do not require a change in the medical care funding system:

a) *Laws to protect insurability*: Several laws have been passed in the U.S. and additional ones are being considered that progressively attempt to protect the insurability of individuals with genetically transmitted disease. A discussion of these laws and proposed legislation is beyond the scope of this document, however, most of these laws have sufficient exceptions that render them less effective. Singapore is in the position to decide its legislative approach to genetic insurability. A key principle should be that individuals cannot be denied the right to medical care simply because of his/her genetic history. This can be accomplished by prohibiting insurance companies from denying insurability for those testing positive for a genetic disease, or for those with family histories of genetic disorders. Companies should not raise the premiums for those genetically at risk as an indirect means to drive these high-risk individuals out. Without some form of protection, the use of genetic testing to best determine at risk populations will not be socially feasible.
b) *Remedies for breach of Confidentiality:* Plaintiff may obtain an injunction to stop publication or prevent further publication of the confidential information. It is however, important to rigorously define confidentiality such as the assignment of identifying variables so that the person can be easily selected from a crowd. With repeated breaches of confidentiality, the investigator may have his/her rights as an investigator revoked and their ability to write for research grants removed.

Certificates of confidentiality: Even if no laws can be passed that will protect the insurability of individuals, there should be at least some form of legal protection for participants in genetic research. In the United States, research institutes may request from the Department of Health and Human Services, a Certificate of Confidentiality. Such a certificate protects the institution from being forced to release socially sensitive information obtained during the course of biomedical research even when subpoenaed. Originally established to protect against

enforced disclosure of personal drug and alcohol history, the use of Certificates of Confidentiality have been expanded to include AIDs research and genetic research. This adds an element of security to the research participant that his/her personal information cannot be extracted without their permission. We recommend that Singapore adopt, as a minimum, such a legal mechanism to protect against enforced disclosure of research information.

The operational implementation of such a certificate system is as follows: A research center applies to the central IRB governing body for a certificate of confidentiality. In this application, the purpose, a short description of the project and of the methods to ensure confidentiality are provided. The IRB approved protocols are appended.

4.5 *Clarity of purpose/Know what we are governing*

My major criticisms of the recent U.S. system governing tissue and DNA research have been that the regulations do not recognize the differences between the varying forms of tissue/DNA based research and that there have been no definitive structural mechanisms within the IRB system that seeks to resolve overarching conflicts and controversies. Such differences include: somatic vs. germline DNA investigations, and studies involving highly penetrant genetic states vs. those with low attributable risk. As these research regulations became more confusing for IRBs and researchers, conflicts arose between these communities. The central regulatory bureaucracies adopted a stance of non-interference referring to the importance of local IRB control. Local IRBs were given no guidance as they struggled with interpreting the complexities of the new science and ambiguous laws. Into this leadership void came the special interest groups both outside and within the government thereby politicizing the issues. Thus, understanding and acknowledging the differences in research domains (i.e., somatic vs. germline) is an important first step in formulating solutions.

4.6 *Clarity of Purpose/Black and white and then the gray: informed consent and reconsent*

Central to the current tissue research controversies has been when informed consent/reconsent is required. The NBAC (U.S.) has promulgated central guidelines that are very reasonable:

"NBAC proposed process for research using human biological materials incorporates these categories to determine if the research is subject to human subjects regulation and IRB review. If the samples are are publicly available, unidentified, the subject is deceased or the process of unlinking the samples is sound, the samples may be legally used without informed consent or IRB review (although a designated IRB person must help to make this decision). If the samples are **coded or identified** the research is subject to human subjects regulation and IRB review (see Chart 1, Appendix D of NBAC Volume I, p 106). It is then determined whether the research is eligible for expedited review and if informed consent is needed, both of which are based whether or not the research is minimal risk. If minimal risk the research is eligible for expedited review. If waiving the informed consent will not adversely affect the subjects' rights and welfare, then no informed consent is required."

We believe the operational problem in the U.S. following the NBAC report will be in regulating the use of coded samples, a debate that have already been politicized by earlier processes. We propose to further clarify with the following extended guidelines:

4.6.1 The informed consent and reconsent are required when therapeutic interventions, physically accessing new tissues for research, or new information gathering requiring direct patient contact are considered.

4.6.2 Informed consent and reconsent are required if the research on archived samples seeks to test germline mutations in highly penetrant phenotypes, and to link these results to clinical data and patient identifiers.

4.6.3 Informed consent and reconsent/IRB review are not required when samples are anonymized.

4.6.4 Informed consent and reconsent can be waived:

4.6.4.1 If the patient will not be recontacted and if the test does not involve interrogation of germline DNA mutations associated with highly penetrant phenotypes.

4.6.4.2 If the linkage between the patient identifier and the test outcome can be sufficiently obscured by electronic means and the use of Data Escrow agents. This guideline specifically permits the use of coded information without informed consent or reconsent since the primary investigator will not have access to unique identifiers of each patient. It is therefore important for the Singapore BAC to clearly define the acceptable parameters for such a Data Escrow interface.

4.7 *Continuous learning and forums for conflict resolution*

The various IRBs function as a democratic forum for citizenry to inject their ethical sensibilities into the research activities of a country. As such, they form an invaluable forum for public participation and feedback. However, as local forums, they cannot be expected to work in isolation promulgating decisions on topics of extraordinary complexity. We therefore recommend that formal mechanisms be developed:

4.7.1 Whereby the local IRBs can be linked to the activities of the BAC and that a continuous dialog can emerge between the national and the local bodies empowered to oversee research ethics;

4.7.2 Whereby the local IRBs can meet with other IRBs, perhaps yearly, to learn of new scientific methods, to discuss issues of concern to them, and to dialog with the scientific and regulatory communities;

4.7.3 Whereby the IRBs can learn of decisions by other IRBs concerning research touching on interesting or sensitive ethical or operational issues. A central body such as the BAC may use this as a mechanism to keep in touch with the pulse of the country, and as a means to test consensus in the community. To this end, we believe that such decisions can develop into a body of “case law” to guide, but not to dictate, the thinking of other local IRBs. In this process, interesting and potentially controversial studies and their IRB deliberations can be shared with all Singaporean IRBs followed by an open discussion/comment period. Such “case studies” should be disseminated to IRBs and to institutional researchers on a regular basis and can be used as reference in future decisions.

ATTACHMENT I

{From Grizzle et al. Arch Pathol Lab Med. 123:296-300. 1999.]

In March of 1996, the CAP produced a white paper which was endorsed by 17 pathology related organizations and approved as the official policy of the CAP (draft form not published). In 1999, the authors of the consensus statement revised portions that were being misinterpreted.

Is Genetic Information different than other medical information?

Similar to other groups they grappled with the question is genetic information different than other medical information and determined three characteristics have been proposed to account for that difference: "power, predictiveness and implications for individuals other than the patient. Gostin indicated a qualitative difference in that genomic data unlike other health information are inherently linked to one person. Clayton and Reilly indicated that genetic data may provide information about more than just the individual from whom the data are derived. The CAP group cited that "potential differences in the extent of harm that may result from the misuse of different kinds of medical information and thus there is a need for an operative definition of genetic information . "Information used for diagnosing or treating an inherited disorder or for genetic counseling." "Genetic tests should be defined as tests that provide information used for diagnosing an inherited disorder."

Confidentiality:

Like, NBAC, they maintain that genetic information be "subject to the same standards of privacy, confidentialilty and security as nongenetic medical information." The definition of genetic information focuses on validated medical information, "important enough clinically to warrant counseling patients and their families members as to risks or future disease." They maintain that the "same confidentiality considerations should apply to patient information obtained during the course of research and investigation, even though the information is not part of the medical record. (similar to call for privacy guidelines from elsi, 1999).

CAP contends that "confidentiality means that information will not be disseminate freely" implying a fiduciary duty not to disclose the information to others without the person's consent, actual or implied, or otherwise in his or her interest." They recommend that pathology departments develop written procedures concerning privacy and confidentiality protections, including procedures for releasing information for research. Like OPRR, they recommend coding of data and that research data be stored physically separate from clinical or personally identifying information. Security policy and procedures should be written out.

Research data is not genetic information:
One of the concepts that they brought forward is that research data should not be considered genetic information. "It is important to realize that information developed in the course of research generally is not valid patient information for use in genetic counseling. Therefore research data should not be considered genetic information as that information is used in statutory information. Similar to MacKay's principles of what constitutes information (1984) that is sited in the OPRR Genetic research guidelines (1993).

Misuse:operational challenge is one of security:

"There is no disagreement with the fact that confidential information has been and will continue to be at risk for inappropriate disclosure. The operational challenge is, thus, one of security." "Security is the notion of unlikelihood of undesired disclosure or leakage of

confidential information, intentional or not." They recommend that "organizations and individuals must operate under rules of conduct and use physical systems that reasonably protect this information from inappropriate disclosure." (same principle as NBAC with sound system for unlinking; some of this is addressed with HIPAA regulations"

They contend that samples collected under the stewardship of pathologists (during the course of the clinical care of the patient) are a vital part of the medical record. "The laboratory that provides the primary diagnostic analysis of specimens is responsible for the maintenance and integrity of this part of the medical record". They also assert that is the pathologist's duty and responsibility "to provide appropriate material for research studies that have received IRB review."

"Breach of confidentiality is major risk research subjects encounter when it is possible to link a specimen to a source." Similar to NBAC they suggest that "when information about the specimen sources is withheld from researchers and any link is provided only through *IRB approved confidentiality procedures* , the risk to research subjects from unauthorized breach of confidentiality is minimal." (Again this puts burden of responsibility on IRB to have criteria for approval of mechanisms of security. It may be that HIPAA requirement laid this foundation for "appropriate process of unlinking" (NBAC).)

Recommendations:

Existing, anonymized specimens, should be, for research purposes, treated as anonymous specimens that were never linked to a source as defined by 45 CFR 46. (therefore using the 45 CFR 46 criteria that the specimen cannot be linked and that the specimen is publicly available, it meets to criteria for exemption from IRB review and informed consent). (here anonymized is defined as " where linkages have been removed irreversibly, rendering the specimen equivalent to an anonymous specimen-it this what NBAC refers to as unlinked? How do you remove linkages irreversibly??)

Where the specimens or data are identifiable or linked (where the specimen is coded for research purposes but can be linked to the sources through a code) researchers must agree to prohibitions restricting them from contacting both the patients who were sources of specimens used for research and their families. The prohibition of patient contact does not preclude obtaining information from tumor registries.

Requests for contact of subjects or families must be made through the appropriate IRB. If the IRB approves contact, the IRB should determine the method of contact.

Before releasing specimens to researchers, stewards of specimens should ensure that the researchers have IRB approved research proposals and they have signed nondisclosure statements or have obtained written exemptions from the IRB.

Publications and presentations must not permit the identification of individual sources of research specimens without specific consent of the patient.

In the case of identifiable specimens, it must not be possible, without the patient's specific consent and IRB approval, either for research results to become part of the medical record or for the patient's to be aware of research performed on their specimen. Information developed in the course of research generally is not regarded as valid for the clinical care of the patient, and therefore research results should not become part of the medical record and physicians should not base their care of patients on the results of

research. (but what if this is part of a clinical research trial, where patients are treated based on result of a test -test should be a valid test done in a diagnostic lab).

Penalties: Abuse in research (breach of confidentiality) is best dealt with via sanctions against the offending individuals and institutions.

Ownership:

"If a patient gives his or her tissue specifically for research, it is unclear whether the tissue becomes the property of those to whom it was given." However, they go on to indicate that since the specimen was substantially "transformed from its original state", through the process of fixation and embedding in a was block, "the durable goods thus produced, can fairly be claimed the property of the entity that produced them."

The pathologist "holds the tissue in trust, primarily for the patient but also for society at large."
Consent:

Posit that the consent doctrine criteria described in 45 CFR 46 were intended for application to therapeutic interventions and that "applying this same consent doctrine to research with human tissues, the interests of patients are fundamentally different from those in which therapeutic intervention is at issue" (Yes, but it still boils down to risk and harm and benefit).

Harm in disclosure:
"A single research study does not establish irrefutable scientific fat, and the results of a single investigation have no applicability to an individual patient." "Disclosure of a single research projects results to a patient is at best not beneficial and at worst could be misleading or even harmful."

Future use/current consent doctrine not useful for non therapy research.:
"To give a description of each and every research protocol that might be performed in the (sometimes distant) future on a patient's tissue is an unreasonable burden for the patient and the researcher." The current consent doctrine is not well suited to research that does not involve therapy. Recommend the use of simple consent forms.

Again they maintain that this is use of excess tissue, which is not necessary for the integrity of the medical record and that consent for such donations [of tissue] "should be regarded as sufficient for the protection of patient's rights."

Forms to be worded so patients can agree or disagree to consent for tissue donation. In response to the statement that some genetic research involves greater risk that other medical information--"However the rules of privacy, confidentiality and security should equally apply to all patient information. Genetic information, like other research information, would be adequately protected if the recommendations of this document were followed."

Addressing risk as part of informed consent process:

Risk if primarily social(stigmatization, loss of insurance, etc) and should be addressed through social mechanisms-law, regulations or code. ‘'It is unrealistic to ask patients to foresee all

adverse societal consequences [or investigators for that matter] of research as part of the informed consent process. “Such potential risks should be balanced by the health benefit that will accrue to the population by the research. “

Living vs dead:
Similar to NBAC does not feel that regulations should apply to only living persons, because genetic information can provide info to family members still living. However the CAP group contends that “ if safeguards are in place to prevent unauthorized disclosure of medical information, “ the risk is minimized.

CAP suggests that if tissue is collected specifically for research (not left over) then informed consent is required.

Prospective vs retrospective sample use:

“In prospective studies the research study or protocol was designed an approved prior to the collection of the sample. In retrospective studies, materials are used that have been stored and were originally obtained for diagnostic and therapeutic purposes or obtained for use in a previous research study.”

Simple consent:
“In both prospective and retrospective studies, residual specimens can be made free of identifiers (anonymized or anonymous) or can be made free of direct identifiers (i.e., linkable or coded). We recommend that the appropriate regulatory agency modify the current federal regulations so that simple consent for research should be sufficient for the use of all samples that are anonymous or anonymized”
(here we assume, simple consent means the surgical consent?)

Waiver of consent:
“Provided that the written non-disclosure confidentiality, and security policies have been approved by the IRB, we recommend that the appropriate regulatory agencies should provide guidance to IRB’s to permit broader latitude to waive consent for research on identifiable (linkable or coded) samples. Such a waiver should be granted on a case-by case basis, including assessment, nondisclosure and security policies that adequately protect patients and sample donors from inappropriate disclosure of protected information.”

Note:
The white paper and subsequent revision/clarification has been formally endorsed by 17 different associations including: Academy of Clinical Laboratory Physicians and Scientists; American Association of Cancer Research, American Association of Neuropathologists, Inc,. American College of Veterinary Pathologists, American Registry of Pathology, American Society of Investigative Pathology, American Society of Clinical Pathologists, American Society of Cytopathology, Arthur Purdy Stout Society of Surgical Pathologists, Association for Molecular Pathology, Association of Directors of Anatomic and Surgical Pathology, Association of Pathology Chairs, College of American Pathologists, Society for Hematopathology, Society of Toxicologic Pathologists, United States and Canadian Academy of Pathology, Universities Associated for Research and Education in Pathology.

ATTACHMENT II
[From Lynn Dressler, University of North Carolina, Chapel Hill (copyrighted). Not to be reproduced without permission]

According to NBAC and modifying from OPRR, the research must first be defined as human subjects research. NBAC does not feel that anonymous samples which represent minimal risk should be considered human subjects and therefore are not regulated by 45CFR46, however most feel IRB review is warranted to ensure sound science. Also if individual is deceased AND the research will not adversely affect any family or community, the research is not considered human subjects by NBAC and OPRR.

Definition of a Human Subject:
In order to decide if human subjects regulations and IRB review applies to the research, the definition of a human subject is required. NBAC indicates (Chart 1, p106) that if the human samples are coded or identified then the research is subject to the Common Rule and IRB review. According to NBAC recommendations, samples that can legally be used without informed consent or IRB review include the following kinds of samples:

-samples that are publicly available1
-samples that are unidentified (anonymous)
-samples from deceased subjects2
-identifiable samples, where the process of unlinking the samples is sound3

Well known sources of publicly available information include telephone books and land title records. It is not clear what kinds of biologic materials might be considered publicly available. OPRR's definition, "unrestricted access on demand (ie unrestricted availability subject to only limited quantities and/or related cost)", is still unclear and provides little guidance.
Although, both NBAC and OPRR (now OHRP) have indicated that a deceased individual is no longer considered a human subject, NBAC further clarifies that if the research would adversely impact the deceased individual's family or community, then the research needs to be considered regulated by the Common Rule and subject to review by an IRB to determine level of risk. For example, this might well relate to certain types of genetic research such as studying a specific mutation in the BRCA1 gene believed to be more common in Ashkenazi Jewish women.
How one determines that the process is sound is currently up to the IRB's to decide. There are certain models that may be helpful to promote as examples.

OPRR GUIDELINES (45CFR 46):
What is a human subject?

As defined by OPRR (Chart 2, p107), the definition of a human subject must meet the following criteria: "Is there an intervention or an interaction with a living person that would not be occurring or would be occurring in some other fashion but for this research? " If the answer to the questions is yes then human subjects are involved and the Common Rule applies for informed consent and IRB review unless the criteria for exemptions are met. If the answer to the question is no, but the answer to the following question is yes, Will identifiable private data or information be obtained for this research in a form "associable" with the living individual, then human subjects are involved and one must follow the Common Rule or meet exemptions. If however, the answer to both of these questions is no, then the Common rule does not apply and the research is not considered human subjects research.

ATTACHMENT III

[From Lynn Dressler, University of North Carolina, Chapel Hill (copyrighted). Not to be reproduced without permission]

Guidelines for DNA Banking:

Testing of DNA began in the early 1960's, with newborn screening for phenylketonuria (PKU). However , at that time, few laboratories were actually involved in the process of banking. "DNA based presymptomatic, predictive, and identity testing has spawned new practices: DNA banking (the long-term storage of cells, transformed cell lines or extracted DNA for subsequent retrieval and analysis) and DNA data banking (the indefinite storage of information derived from DNA analysis, such as linkage profiles of persons at risk for Huntington's disease." [Philip Reilly, AJHG, 1992). Today, academic centers, private and commercial organizations, bank DNA for medical as well as research purposes. In addition, several other resources constitute "virtual" banks of DNA, including Guthrie cards, (dried blood spots from newborn screening from which DNA can be extracted) and surgical pathology blocks (tissue specimens obtained at the time of surgery, preserved in fixative and embedded in wax blocks for long term storage).

Currently, however, the largest banks of DNA are associated with forensics and the military, for the purpose of identification of individuals. In 1996, 40 states had statutes to establish state forensic DNA banks, 32 of which had already begun to collect samples, totaling nearly 400,000 samples [Jean McEwen]. The Department of Defense had already collected 1.5 million samples at that time, with the expectation that the bank would be complete by 2001, containing 3 million samples. A federal law passed in 1994, the DNA Identification Act, helped to fund forensic DNA analysis activities [DNA Identification Act of 1994, Pub. L. No.103-322, 108 Stat. 1796S21304 (1994)] and a computer network, CODIS, (Combined DNA Identification System) was authorized by the Federal Bureau of Investigations to enable exchange of forensic DNA information between the data banks in the different states [42 U.S.C.S 14312 (1994)]. This law provides some privacy protections as well as criminal fines for violating these protections. Specifically, the law " requires crime labs , as a condition of participating in the CODIS network, to limit disclosure of stored individually identified DNA samples and data to criminal justice agencies, for law enforcement identification purposes" [DNA identification act]. Thus there is an infrastructure in place for DNA banking. It includes not only collection of specimens or DNA (DNA bank) , but the storage of data derived from the analysis of the DNA (DNA databanks) and the opportunity to share this data electronically. However, except in the forensic context, most DNA banks and DNA databanks established for medical, research, or commercial purposes are largely unregulated.

There have been, however, several groups in the United States and elsewhere who have suggested guidelines for establishing and maintaining DNA banks. Most of these guidelines focus on banks of samples rather that banks of data and include ethical as well as practical recommendations. The following parameters are common to most all guidelines: 1. Samples should be coded with an identification number to protect the identity of the DNA source; 2. The bank must provide provisions to allow an individual to remove their DNA or have their DNA destroyed should they decide at some time in the future not to continue to be a participant in the bank; 3. The bank should indicate to the DNA source how long the DNA will be stored and 4. The bank should have a plan for the future of the bank, in the event that the laboratory or company currently responsible for the bank is no longer funded or in operation.

Most all guidelines address the concept of informed consent or waiver of such, but the criteria for requiring consent or waiver are not uniform. Most all guidelines include some aspect of access to samples, however there are major differences from group to group, especially for

the use of specimens for future, yet unspecified genetic research. Some guidelines indicate that for each intended use or study, recontact of the individual for consent is a requirement, unless the DNA is completely anonymous; other guidelines indicate that the general nature of the future research must be indicated in the informed consent, eg. that future research includes only cancer -related studies or will not include studies of social behavior or intelligence.

ASHG: Points to Consider

In 1987, recognizing the medical importance of DNA analysis information, the American Society of Human Genetics Ad Hoc Committee on DNA technology published their official "DNA Banking and Analysis Statement" [ASHG statement]. Their "Points to Consider" guidelines were geared toward " banking for the preservation of DNA needed for analysis at a future time." The ASHG indicated that differences existed between DNA analysis for clinical purposes versus other clinical genetic tests at that time, specifically, 1. "The long term stability of DNA may permit questions to be answered later that were not envisioned at the time of its procurement; 2. Since DNA analyses commonly involved linkage analysis, a concept that is unfamiliar to laypersons and to many health care professional, there is significant risk of misinterpretation of results by recipients and 3. The rapid advance of DNA diagnostic capabilities places special responsibility on the providers of these services to keep current." These concepts still apply today.

Although these guidelines were referring to the clinical context, they are still relevant in the research setting.

There are 11 points to consider in this document including appropriate submission of samples, ownership of DNA, banking policies to inform the depositor, disclosure of results, transfer of data, accuracy of test result, quality assurance practices for the lab and competence of the director,secondary use of samples and the role of the ASHG in this process:

Submission of samples to the bank or diagnostic laboratory:

The recommendation is that DNA banks or diagnostic laboratories accept samples and requests for analysis only from health care professionals and not from individuals or families "without the mediation of health care professionals." This guideline places responsibility on the health care provider to provide appropriate quality control and quality assurance, including determining the nature of the genetic information that is needed by the family and if DNA analysis is likely to provide this information; interpretation of results and counseling individual/families regarding significance, accuracy, "attendant risks, such as identification of non-paternity". The health care provider would also facilitate sample collection from the individual and other family members as needed. A genetic evaluation should precede banking of any DNA. The health care individual assuming this responsibility would need to be knowledgeable about human genetics and the nature of these tests. This last point may seem obvious, however, even today, DNA analysis is requested and results interpreted by health care professionals who may not be competent to do so.

Ownership of the DNA in a bank:

"The banked DNA is the property of the depositor, unless otherwise indicated." The depositor is not considered a "donor", which implies gift.

Written bank policies to avoid misunderstandings between the depositor and the DNA bank:

A written document should be used to inform the depositor of the bank's policy prior to the individual submitting a sample . It is recommended that the document contain the following information: "services provided, duration of storage, disposition of the DNA at the end of the agreed upon time of storage or upon death of the depositor, conditions

under which the DNA can be used for purposes not requested by the depositor, eg. research, a discussion of risks associated with banking, such as loss of samples; an agreed upon method of maintaining contact between the depositor and the bank.

Release of DNA analysis results:
Results of DNA testing should be released " to the appropriate health care professional, who has the responsibility of informing the patient or family of the results and their meaning". This allows only those individuals (of the family) who want the results to get the results. The guidelines indicate that the "results of the tests should be subject to the traditional principles of medical confidentiality and should be released to third parties only with the express consent of the individual ". ("Express consent" is not further defined as written or verbal).

Transfer of DNA to a third party:
The laboratory must obtain "express consent" before transferring DNA to a third party. However they do include the caveat that "unless immortalized cell lines have been established, patient DNA is exhaustible, and the patients needs should take priority". Here the concern was not so much a legal/ethical issue but a practical issue.

Accuracy of the reported result:
At the time of these guidelines, most DNA testing results were given as DNA linkage results. The ASHG recommended that these results be reported in terms of probability of a disease carrier state" (to the health care professional who submitted the sample). The DNA analysis laboratory is responsible for error "due to improper laboratory technique or due to improper estimate of disease likelihood." The lab is also responsible for requesting another sample if " the DNA sample is lost or found to be unsuitable" for analysis. The health care professional is responsible for an error "due to an incorrect statement of genetic relationship of family members.

Secondary use of the sample.
The deposited DNA can only be used for purposes unrelated to the original request of the depositor with the express consent of the depositor. The depositors desires should be determined at the time the sample is collected. (Process for "express consent" is not defined).

Minimal standards for quality assurance.
Several practical aspects for running a DNA bank are indicated: a DNA bank should occupy separate space from other DNA work, have secure, alarm-equipped facilities. A lab should have a written manual of procedures and training of personnel in meticulous technique. Samples should be coded "so that a minimal number of individuals have access identity of the depositor. Written records should be maintained to track the receipt, disposition and storage of each sample. They also recommend dividing each sample and storing in two physical separate places. Control samples should be analyzed before deposit to ensure integrity of sample, and at periodic intervals of storage (to determine that RLFP patterns are not affected by storage).

Competence of Laboratory Director/Certification of Directors.
ASHG recommends and endorses a certification program for directors of DNA banks and DNA analysis laboratories, which involves "analyzing test samples and providing appropriate risk assessments based on the test results."

The ASHG role in "ensuring that banks meet patients" was to publish these recommendations, support the certification program mention in point 9 above. "advocate

accessibility of testing to all who would benefit", take a lead in education of health professionals and address ethical and social policy issues. Since the publication of these points to consider the ASHG has published a statement on Informed Consent for Genetic Research (1996) based on level of anonymity and study design (retrospective versus prospective).

Robert Weir, DNA Banking and Informed Consent:
Specific recommendations for informed consent for DNA banking in the research context were published eight years later in 1995, in the journal**, IRB, A review of Human subjects research** . These recommendations were based on the results of an ELSI project conducted at the University of Iowa. Bioethicist Robert Weir and associate Jay Horton evaluated 79 consent forms from 50 investigators in 25 states that responded to a letter sent to 155 randomly selected genetics investigators who were members of the American Society of Human Genetic (ASHG). The 24 consent forms that related to DNA banking were used in their study. Seven categories of content was used in the evaluation of the consent forms and form the basis of the subsequent guidelines, including : confidentiality and privacy, control and ownership of biologic materials, withdrawal from the research study, length of storage, future access to genetic information, future third party access, and secondary use. Their contention was that all seven categories should be addressed in a consent form relating to DNA banking and yet they did not find any one form addressing all these areas.

Confidentiality and Privacy.

"Stored biologic materials (tissues, DNA samples, cell lines) and derivative genetic information need to be kept confidential: authorized access to the materials and information is limited to and by the investigators and lab personnel anticipated in the agreement with the sample source; and private: unauthorized access to the materials and information by persons without a professional need to have access is limited by physical and computer security measures."

Control and Ownership of the banked biologic materials.

The consent document should address the investigator's plan for banking, including the possibility of a creating a cell line and address related issues of control, ownership and possible financial profit (eg. the transformed cell lines may be patented and become reasonably profitable). Their suggestion is that "the consent document interpret research participants and investigators as being **sequential owners** of the original tissue sample or cell line and that the research participants be promised a percentage, perhaps 10-25% of any profits resulting from future use of the cell lines." They also offer an alternate process, whereby the investigator would reconsent the sample source if a cell line turned out to be commercially valuable. " A disclosure statement along these lines, is, we think, mandatory in consent documents for DNA banking when the source of the tissue sample is likely to remain identifiable and/or when the investigators who secure the tissue sample decide to transform it into a cell line." They further indicate, however, that, if the sample source is anonymous or "truly anonymized" ("so that no subsequent identification of or link to the sample source is possible) and that the investigators do not anticipate any commercial possibilities, the disclosure statement can be omitted from the consent. Nineteen of the 23 documents evaluated did not mention the issue of ownership.

Withdrawal from the research study.

Consent documents frequently address a participants subsequent decision to withdraw from the study. The authors point out thought **that "in genetic studies that involve future**

research on stored material , the issue of withdrawal concerns not only the withdrawal of a participant from a study, but also the decision regarding his or her **continued contribution to** (eg tissue, blood, DNA, cell line) **or personal identification with** an ongoing research project using banked samples."

They recommend that the withdrawal from a study using DNA banking can take two forms: "1. The possibility of participants subsequently requesting that their stored biologic materials be destroyed and/or 2. The possibility of participants subsequently requesting the anonymization of the DNA samples.

Length of storage.

The consent document should indicate how long the investigators plan to store the DNA, rather than suggesting that the materials will be stored for an indefinite period of time, eg. an arbitrary number of years or the period funded for the research. "Either way, investigators would convey a sense of certitude, structure, scientific goal and control to potential research participants, rather than a sense of unplanned, unstructured guesswork about future research." The authors state further, however, "the necessary indefiniteness of research time on immortalized cell lines is different from the time-limited research that is possible with stored tissue samples."

Future (participant) access to genetic information:

The authors first address a research participants "right to know" or "right not to know" personnaly relevant information gained from the study . "The expectation is grounded in personal autonomy, the right of self-determination and more specifically the right to be informed, at the completion of the research project regarding any information that has been learned that would be of clinial erelvance to therm or that would be relevant to major decisions they face concerning procreation or appropriate health care." The authors recommend that language in the informed consent indicate that potential research participants have a choice to make-to have access or not to information gained from the study that has "clinical relevance to them." If the participant chooses to be informed, consent documents should indicate the policy of such disclosure: "1. Interim results and/or incidental findings (eg false paternity) to research participants.

Future third party access:
In their study, 20 or 23 documents made no reference to third party access to banked biologic materials or personal genetic information. The authors include family members, employers, insurance companies, government agencies in this category. Although they make no definitive recommendation, the authors suggest that research participants might be interested in restricting this type of access without written consent from the individual participant or their legal representative.

Secondary use of genetic information:

Secondary use was defined by the authors as :" 1. Use of tissue samples or cells lines secured for one genetic study by the principal investigator but for another scientific study with another scientific purpose; or 2. Use of the tissue sample or cell lines by other investigators in the PI's laboratory for different scientific purposes than the original study; or 3. Use of the tissue samples or cell lines by other investigators outside the PI's laboratory but for the same research c purpose; or 4. Use of the tissue samples or cell lines by other investigators outside the PI's laboratory for different scientific purposes."

Because of “the frequent practice of secondary use and the limited awareness of the practice by persons outside the biomedical field”, the authors recommend that “consent forms for genetic research should adequately inform potential research participants about secondary use.” The authors suggest three ways this can be accomplished ”by assuring potential research participants that there will be no secondary scientific use of their stored biologic material; by giving them the option of consenting now to future secondary use of their DNA sample , or by promising them that they will be recontacted for consent if the investigators subsequently decide to make secondary use of the stored sample, especially if the purpose is different than the original research study. “

Another publication from the United Kingdom shows a sharp contrast to the recommendations of the US organizations. For example, for service (or clinical) work, consent, either verbal or written was not obtained prior to blood collection or DNA banking, although the purposes of the investigation were explained to participants. For research purposes, verbal consent was recommended and “ in some circumstances, written consent.”[Yates et al , 1989]. Most the research activities at that time were focused on single gene disorders such as Huntington’s chorea, cystic fibrosis, neurofibromatosis, Duchenne/Beck muscular dystrophy and haemophilia. It is important to note, however, that these guidelines, which were published in 1989, focused on practical aspects of quality assurance, ensuring that each specimen could be correctly identified and tracked to the appropriate family. Yates and colleagues specifically indicated that “medicolegal [or ethical issues] were not being considered.” Other issues brought up in this article were the possibility of a national registry of data, to ensure a centralized monitoring of information and banked DNA for future use by the family.

The most striking example of a national repository is that which has been developed in Iceland.

Discussion of George Annas article-privacy rules for DNA databanks
Protecting coded Future Diaries:

George Annas has likened DNA databanks to “an individuals probabilistic *future diary”,* arguing that genetic information is different from medical information, because the information contained in the DNA is “*more sensitive, written in a code that has only been partially broken and contains information about an individual’s parents, siblings and children.*”(Annas, JAMA, 1993). He further argues that “ current rules for protecting the privacy of medical information cannot protect either genetic information or identifiable DNA samples stored in DNA databanks ”and that the decoding of the human genome “will lead us to alter radically our view of privacy.” Although he suggested that optimally we should have a moratorium on DNA banking until reasonable rules are developed, and that either uniform state laws or federal legislation should be developed, he conceded that these possibilities are unlikely. He therefore recommended voluntary agreement on DNA banking rules and recommended overall that a “DNA databank licensing board be established to license all DNA databanks in the US with uniform rules. Specific recommendations for consideration included the following four areas:

> No DNA databank should be created or begin to store DNA unless three criteria are met: a) public notice that a DNA bank is being established and the reason for the bank; b) a privacy impact statement prepared and filed with a designated public agency that is responsible for developing and enforcing privacy guidelines for a DNA bank; and c) burden of proof should be on the DNA bank to establish that storage of DNA molecules is

necessary to achieve an important medical or society goal.

No collection of DNA for storage is permitted without written authorization and agreement that: a) sets for the purpose of the storage; b) sets forth all uses, including any and all commercial uses; c) guarantees the individual: I) continued access to the samples and all records about the sample; ii)the right to correct incorrect information; iii)the absolute right to order the destruction of the sample or its return should the DNA bank significantly change its identity or cease operation.

DNA samples can only be used for the purposes for which they were collected, and linkages to other computerized information systems are prohibited. Specifically: a. no waivers or boilerplate statements, b. no access to DNA information by any third party without written authorization; no access by third part to any identifiable information; d. strict security measures, including criminal penalties for misuse or unauthorized use of DNA information.

Mechanisms developed to notify and counsel those whose DNA samples are in storage when new information is that can have significant impact on their health is obtainable from their stored DNA.

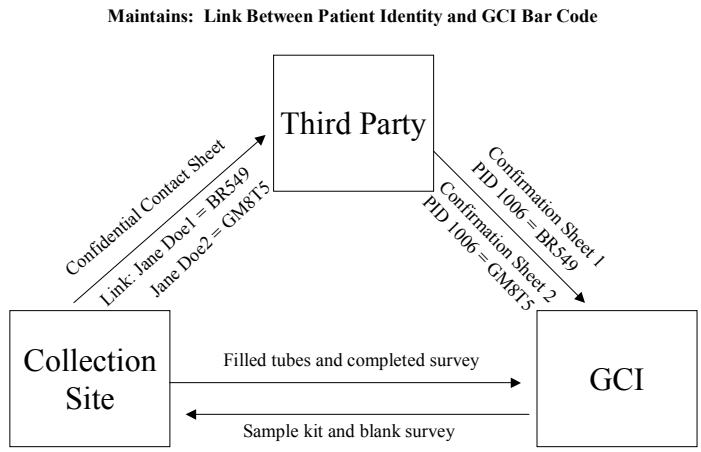
ATTACHMENT IV
Data Storage & DNA banking for Biomedical Research from the Public & Professional Policy Committee of the European Society of Human Genetics (ESHG)

Please refer to:
http://www.eshg.org/Banking%20background%20consult.pdf

ATTACHMENT V
Genomics Collaborative, Inc. Third Party System

In this plan, the third party will serve as an escrow agent and will be responsible for maintaining the link between the GCI bar code and the patient identity. Neither GCI nor any other party is allowed access to this link. GCI can request (for itself or on the part of the FDA or a customer) additional information about a specific donor or may request duplicate information from a specific donor to validate GCI's data collection process through the Third Party.

Longitudinal Collection Methodology



Maintains: Consent Forms Interaction History

Jane Doe	Collection 1 9/9/99
	Collection 2 9/9/00

Maintains: Case Report Forms and Samples identified by GCI bar code

Site #	Patient ID#	Sample ID #	Date Collected	Data
CC-345	1006	BR549	9/9/99	1,0,1,0,1,0
CC-345	1006	GM8T5	9/9/00	1,0,1,1,1,0

The interactions between the collection sites, Third Party, and GCI are illustrated below.

Initial Collection

GCI sends out kits and case report forms to participating sites

Physician identifies patients, completes consent, confidential contact sheet, case report form and blood collection

Physician retains a copy of the consent form and records name and date of collection for the individual who has donated, retaining this information in his/her office (not in the donor's medical record).

Physician sends completed case report form and sample kit, identified by GCI bar codes, to GCI

Physician sends the confidential contact sheet connecting the GCI bar code number and patient name to Third Party.

Re-Contacting Patients

In the event that GCI requires additional data and/or samples from specific donors:

GCI would supply a list of sample ID numbers requiring follow-up to Third Party and supply new case report forms to the collection sites that originally collected the samples.

Third Party will contact collection sites indicating patients require followed up

Physician will send completed case report forms (with an additional sample, if required) to GCI using a new sample ID number

Physician sends link between new sample ID number and patient name to Third Party

Third Party will send the link between new sample ID number and the previous sample ID number to GCI

GCI links new case report forms to existing case report forms.