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NHRPAC Working Group on Genetics
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Glossary

6/27/02: I.C. pharmaco*genetics*; III. B and C: *traits and diseases*
6/28/02: III: add *"and considerations"*
7/02/02: II.A. delete "investigators, subjects, and third parties"

I. Introduction and Definitions

A. General comments

During the past two decades research in human genetics has expanded exponentially in response to the "*molecular revolution*" in our genetic technologies. This revolution has generated significant issues about how we should use our molecular powers and how we should manage and protect personal genetic information that can have both economic and psychosocial impact. The speed and accuracy with which we can now generate vast arrays of genetic information has broad implications for privacy and personal autonomy. Indeed, how genetic information is handled can affect relationships within individual families as well as critical interactions among other individuals and with institutional third parties, including insurers and employers. In addition to personal implications of genetic information, genetics research aimed at developing therapeutic interventions must now grapple with intense concerns about the safety of persons who participate in genetics research as research subjects, and sometimes as both patients and subjects when clinical care proceeds in concert with biomedical research.

The *pervasive nature of genetics* is now evident in every aspect of human endeavor. Genetics researchers and their colleagues in the basic sciences and in every medical discipline, including bioethics, debate broadly and continually about the science and the philosophy of applying new genetic information in our everyday lives. Genetics and genetics research now reach into our homes, our diets, and a plethora of consumer products that are now parts of our daily routines. Indeed, what was once an ethereal corner of intellectual curiosity has become a ubiquitous topic of daily public discourse and attention. We continue to expand the scope of genetics research because genetics is a fundamental in the underlying biology of all living things.

For all the molecular and technical innovations, however, the development of treatments and cures for genetic disorders continues to lag at a cautious pace. As technical advances have generally outpaced applications in treating genetic disease, this *therapeutic gap* has been a source of consternation, even helplessness, on the part of families who are hoping to counter the deleterious effects of their own genetic legacies. The tragic death of a young man who volunteered in 1999 for a clinical trial to treat a serious enzyme deficiency underscored the need for caution in applying new knowledge to human health problems.

The continuing flux in knowledge of genetics and genetic health problems indicates that *Institutional Review Boards* must remain flexible but nevertheless thorough in evaluating genetics research at the local institutional level. IRBs are charged with requiring individual investigators to be complete in crafting their proposals, with due consideration to possible pitfalls in the conduct of genetics research and in communication with subjects and their families. IRBs and investigators are urged to cooperate in developing research protocols that protect the rights and interests of research subjects and their families. Such cooperation may include workshops that

address standards and requirements for human genetics research. IRBs are urged to draw on the resources of lay organizations, volunteers, consumer groups, and parent support groups as sources of thorough, first hand information about specific diseases and disorders and as liaisons between professional researchers and potential research subjects. Finally, in addition to calling on external consultants, IRBs must acknowledge an internal responsibility to assure the competency of IRB members to review research protocols in human and medical genetics.

B. Issues in gene therapy

The focus of this chapter is the general spectrum of genetics research in the biomedical sciences. Because of the nature of issues and applications in the field of gene therapy, these topics are addressed in Chapter xxx of this Guidebook.

C. Definitions

The following definitions are intended only as an introductory guide for non-geneticist members of IRBs.

Proband: the individual who first comes to clinical attention and who serves as the impetus for further investigation of a genetic condition in his or her family

Genotype: the genetic constitution of an individual

Phenotype: the physical manifestation of a particular genotype; what can be seen or measured

Allele: alternate forms of the same gene

Locus: designation of the position of a gene on a chromosome

Linkage: position of two genetic loci measurably close together on a chromosome; statistical proximity of two loci that are transmitted together more frequently than chance would allow, in which one locus may serve as a marker for the other

Association: the presence of an allele in increased frequency in affected subjects compared to control subjects

Monogenic disease: a disease caused by allele(s) at a single locus

Multigenic trait: a trait caused by influences of genes at 2 or more loci

Complex disease: disease that is influenced by gene-gene interactions, gene-environment interactions, and/or other confounding factors

Pharmacogenetics: the study of genetic variations that influence responsiveness to pharmacologic therapies in terms of safety and efficacy; infers a very broad genetic overview

Bioinformatics: computational aspects of genetics, using large databases to aid in understanding biological phenomena

II. General Considerations for IRBs

A. Parties in genetics research

Contemporary research in human and medical genetics represents significant teamwork among members of the scientific community and the individuals and families who participate as subjects. On the scientific side are principle investigators, their co-investigators and other professional colleagues who contribute to the research efforts from their own areas of interest and expertise. Research subjects usually include individual probands who are recognized by the genetic traits that bring them to the attention of research professionals. Because genetic traits may appear in several members of the same family, other family members, including close as well as distant relatives, may elect to enter a research protocol as subjects as well.

A more detailed discussion of the parties to biomedical research is found in Chapter xxx of this Guidebook.

B. Subject recruitment and retention [1] [45 CFR § 46.116]

In *family studies*, the familial nature of research cohorts requires that recruitment procedures avoid undue influence in an individual's decision to participate. The very nature of this type of genetics research exerts at least some pressure on family members to enroll because studies that include complete information across the whole family are more reliable than those based on incomplete information.

While most family studies begin with a proband who presents for evaluation, subsequent recruitment strategies vary. Each has its own strengths and weaknesses, but each may be appropriate if justified by the study. (1) Enlisting the *proband* as the point of contact for recruitment insulates other family members from an initial, and possibly intrusive, direct contact by the investigator. This approach does, however, present the risk that the proband may exert undue influence on his or her relatives to enroll in the study. Further, the proband may be reluctant to act as a recruiter because of a personal interest in maintaining his or her health information completely private. (2) Enlisting subjects through *support groups* or other lay organizations is a workable approach that requires these organizations, as well as the investigators and IRBs, to be scrupulously protective of prospective subjects. (3) Contacting potential subjects through their *personal health care professionals* is another approach, but one that must avoid any perception on the part of the subject that health care and benefits might be compromised in the absence of cooperation in research. [2]

[1] The National Human Research Protections Advisory Committee acknowledges current debate on the use of the words "subject" or "participant" . This issue is currently under study by the Institute of Medicine.
[2] A fourth approach of *direct recruitment* by the investigator, based on information provided by the proband, allowed the investigator to contact potential subjects directly by phone or mail, without a prior "introduction" by the proband or support group. Most geneticists do not condone this approach, and under the HIPAA regulations, this method will be disallowed on the basis of privacy considerations. Under the

Not all research in genetics, however, requires participation of family members. Many other normative study designs are also employed. These designs include case-control or placebo-control and treatment comparisons. Genotyping or other gene-based assays are conducted along with the measurement of other clinical and/or physiologic endpoints under study. Recruitment strategies should reflect those currently used for these types of basic, pre-clinical and clinical studies.

In any genetics research, as in all research with human subjects, the IRB must ensure that the recruitment plan minimizes the possibility of coercion or undue influence.

C. Defining risks and benefits

Potential risks and benefits must be thoroughly discussed with prospective subjects. In genetics research, the primary risks, outside of gene therapy, are psychological and socioeconomic as well as physical. IRBs should review genetics research proposals with these factors in mind.

Psychological factors include both disadvantages and advantages related to generating personal genetic information. Disadvantages include the possibility of stress arising from confirmation of future genetic disease and from uncertainties related to changing genetic probabilities and margins of error in the research process. On the other hand, new information can also confer benefits, particularly if uncertainty about future disease is reduced or eliminated, or, conversely, if the information will permit better planning for the future. An especially important aspect of psychological factors is the availability of *competent genetic counseling* for families that are adjusting to new information about their own genotypes: genetic counseling is complex, and it must be provided by persons who are qualified and experienced in communicating the meaning of genetic information to research subjects and to persons who seek genetic testing. Counseling must also be sensitive to feelings of guilt that arise when parents realize the difficult implications of their own genes for future generations.

Socioeconomic factors include both personal risks and risks posed by institutional third parties. Personal risks include stigmatization, discrimination, labeling, and possible changes in relationships among family members. Risks posed by institutional third parties include the possible misuse of genetic information and loss of financial interests, with attendant difficulties in securing employment, mortgages, or health or life insurance. While these issues have received some legislative attention, they are far from settled.

IRBs should consider these and any other perceived risks and ensure (1) that research proposals include clear provisions for adequate genetic counseling, if appropriate, (2) that risks will be disclosed to subjects, and (3) that subjects will be protected against unwarranted disclosures of personal genetic information. These and any other

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HIPAA rules, direct recruitment might be possible if the IRB waives the required patient or subject authorization for the recruitment phase of the study.

appropriate assurances should be clearly stated in the consent forms that are signed by research subjects.

D. Privacy and confidentiality protections

Privacy rules governing biomedical research rely on federal and state laws as well as institutional rules. Beyond these general laws and rules, however, privacy and confidentiality in human genetics research have heightened importance because information about one individual may necessarily have implications for other family members as well. Further, questions about other family members generate information that, in turn, could raise questions about the status of relatives who are not present. While all individuals are entitled to confidentiality of their personal medical or health information, probands who offer family history information convey information that is often "common knowledge" in the family – information that inheres both in the proband and in other family members. Information about relatives remains hearsay until it is independently confirmed, either by other relatives or by direct interaction with the relative. Because of varying perceptions of privacy and sensitivity of genetic information, all family information collected in genetics research should be afforded reasonable safeguards of confidentiality, even to the extent of avoiding disclosure of information about one family member to another.

Investigators who seek contact with other family members are obligated to respect the privacy and autonomy of these individuals. Investigators should therefore contact relatives of a proband only after those persons agree to be contacted. Such contact can be initiated through the proband, or through a patient support group, or through a personal health care professional. The investigator should not contact a remote family member in the absence of such an "introduction." Once a relative agrees to be contacted by the investigator and that contact is then established, the relative becomes a subject and is entitled to the protections of informed consent procedures.

Data that are generated in the course of genetics research should be stored in a manner that protects the identity of human subjects. Further, unless explicitly authorized by the subject, personally identifiable data may be released only to the research subject, or as required by law.

E. Informed consent

The Doctrine of Informed Consent provides the framework for an on-going process that protects the interests of both human subjects and research investigators. In this process the *investigator informs* the subject about the research project, and the *subject consents* to participation in the project. A detailed discussion of informed consent is included in this Guidebook as Chapter xxx.

Specific risks related to informed consent process in genetics research include the issues outlined below. In a thoughtful and thorough process of informed consent, the subjects should appreciate

1. the kind of information that can be expected from the study and when that information may be forthcoming;
2. that they may receive information that they might not want to know or that they may feel uncomfortable knowing;
3. the assurances of the investigator and the institution to protect confidentiality;
4. that information about themselves may be learned by other family members in spite of confidentiality protections;
5. that genetic information generated during the study may compromise their insurability;
6. that actions they may take on the basis of information generated in the study may entail risks, such as failure to recoup testing costs from health insurers;
7. who will have access to medical records;
8. their rights with respect to their tissue samples;
9. the consequences of withdrawal from the study;
10. any costs associated with participation;
11. that the re-use of samples from a population study or newborn screening must comply with the testing described in the original consent document;
12. the concept of the "therapeutic misconception," or the possibility that the study may or may not yield useful information or therapies, either in the present or the future;
13. the possibility of personal implication, or inadvertent identification, if the study or study results, are reported in the public media.

Not all of these concerns will apply to every research proposal in human and medical genetics, and others may arise based on the details of individual proposals. In any event, however, information must be conveyed in clear language, suitable to the age, cultural background, and physical and mental capabilities, of the research subjects.

These procedures seek to encourage trust among investigators, research subjects, and research institutions. The unique aspects of genetic investigations and the possible consequences for entire families make these considerations necessary for IRB attention.

N. Withdrawal from participation [45 CFR § 46.116(a)(8)]

Subjects have a right to withdraw from participation in a research study. Federal regulations assure that subjects are free to withdraw without penalty or loss of benefits to which they are otherwise entitled. Potential issues include handling of data and/or tissue samples in the event of a subject's withdrawal. The implications of withdrawal should be discussed with the subject as part of the informed consent process and set out in the consent form. The issues include (1) whether withdrawal releases the subject

from providing further information or tissue samples, (2) whether the subject's identity will be removed from the research records, and (3) whether the investigators will eliminate the resulting data from the study or destroy stored tissue samples. Indeed, investigators in family studies *may* remove information about subjects, although regulations are not consistent about whether removal of information is required or prohibited. Thus, while some situations in family studies would permit removal or destruction of data at the subject's request, in clinical trials that are governed by FDA regulations, investigators are required to include information about all subjects who have withdrawn from the trial, and destruction of data is prohibited.

G. Vulnerable populations [45 CFR §46.116]

While most persons who participate as subjects in biomedical research are competent to make their own autonomous choices, the research community has recognized several groups whose capacity for self-determination is limited, or even lost. These groups have been designated vulnerable populations because of their limited autonomy. Included among these populations are children, whose competence develops as a process of increasing maturity, persons with some types of mental disability or dementia, and persons with some types of cognitive disorders. Also included are prisoners, whose restricted liberty could expose them to coercion to participate as research subjects, and pregnant women and fetuses, who engender risks that are unique to pregnancy and fetal development.

Since many hereditary traits and diseases are expressed, at least in part, in diminished capacity, IRBs should carefully evaluate the groups who are proposed as subjects in genetics research. Persons with diminished mental capacities or competence must be carefully protected in communications between their legally authorized representatives and the researchers investigators. In appropriate circumstances, IRBs may consider granting waivers of consent or modifications of the consent process according to established federal guidelines. [Federal Policy § ___.116(d)]

H. Research involving named populations and the value of community consultations

Because some genetic diseases appear with greater frequency in specific subsets of the population, researchers understandably want to focus their research on those diseases within those named populations. This occurs, for example, with sickle cell anemia among African-Americans and with Tay-Sachs, familial disautonomia, BRCA1 and BRCA2 among Ashkenazic Jews. While the research on such named populations may and should go forward, an IRB must take precautions that such research does not unintentionally brand the named population as an inherently sick population. It may do that by any or all of several methods. For example, it might require that researchers reporting their results note carefully that many of these diseases affect only a small minority of the targeted population, albeit a larger percentage than in the general

population. Another way to mitigate this concern is to ensure that other targeted research is conducted on other subsets of the population, either at the same facility or elsewhere, so that no particular group is labeled as uniquely affected.

I. Publication practices

Publication of research data and/or pedigrees may result in identification of research subjects and third parties. IRBs should evaluate whether publication of data and/or pedigrees is essential to conveying the scientific message. If risk of identification exists, subjects must be informed of these risks and must consent in writing to release of such information. Subjects should also be informed that some research may be reported in the media, with the attendant implication of public identification of other family members as well. This issue continues the conundrum of who determines the risk of identification, and on what grounds, and who should be defined as subjects.

III. Approaches in Genetics Research

Family studies

Pedigree studies are a significant foundation of research in human and medical genetics. Documentation of family histories leads to finding and tracking genes as they are transmitted through generations in the same family. To this end, the meticulous construction of pedigree charts is essential to accurate collection and analyses of genetic data.

As geneticists embark on family studies, they gather information, usually first from the individual proband who comes to clinical attention, or from the immediate family. The information serves as a basis for deciding whether to pursue a scientific inquiry. Information about other family members who have, or may have, the trait or disorder includes identification of relatives, both vertically and collaterally across the family structure.

A critical caveat in amassing pedigree information and in constructing pedigree charts is respecting the sensitivity of personal information that is offered by persons who are interviewed. On occasion the investigator will be made aware of unusual family relationships, including paternity and adoption issues that may not be common knowledge in the family. Further, while individuals may discuss their genetic disorders closely with an investigator, they may prefer complete privacy with respect to other members of their family knowing about their health concerns. For these reasons the information recorded in pedigree charts deserves close attention to confidentiality.

Twin studies represent another approach to genetic studies of the relative contributions of genetic and environmental influences in determining the phenotype of an individual. There are two types of twins, monozygotic (one-egg, or MZ) and dizygotic (two-egg, or DZ). Because MZ twins are identical at all genetic loci, any observable differences between MZ twins are theoretically attributable to environmental influences. DZ twins, on the other hand, are related genetically only as full siblings, so that differences between them may be attributed to genetic differences, environmental influences, or both. Twins may be concordant, or alike, for a trait, or discordant, or unlike. Comparison of concordance rates between MZ and DZ twins gives a measure of “heritability,” or the relative contributions of genes and environment to complex traits. The difference in a trait between members of twin pairs can also be compared to the difference of the trait between unrelated persons, as can differences between twins who are reared together or reared apart.

A third approach to family studies is *affected sib-pair analysis*, in which the inheritance of a particular marker allele is followed in pairs of siblings who are affected with a disease. If these siblings inherit a particular allele more frequently than chance would allow, there is an indication that the allele, or its locus, may be involved in causing the disease.

Monogenic traits and diseases

Monogenic, or single-gene, diseases are caused by the effects of a single allele, or a single pair of alleles, both at one genetic locus. While some loci are characterized by many alleles in the population, any one individual will have only two alleles, one inherited from the father and one inherited from the mother. As molecular testing has become increasingly sophisticated, the determination of exactly which alleles an individual carries may give reliable *predictive information* about the *diagnosis and prognosis* of an inherited disorder. Continuing research aims to identify additional genes and alleles over a vast array of genetic loci, with significant potential clinical applications reproductive medicine.

Testing for single genes is also integral to *preimplantation diagnosis and prenatal testing*. For persons at known risk for having children with a defined genetic disorder for which testing is available, the option of in vitro fertilization and embryo transfer presents the opportunity to test very early embryos for deleterious genotypes, so that only embryos lacking those deleterious genes will be transferred to the mother in anticipation of establishing a pregnancy. Similarly, for pregnancies that are already established, prenatal diagnosis can detect deleterious genotypes in the fetus. Prenatal diagnosis has been in place for over 25 years and is ordinarily not a research procedure unless new techniques, genetic tests, or disease states are under study.

For individuals who are at increased risk of being carriers of deleterious recessive genes the option of *carrier testing* is commonly available. Carrier testing for recessive genes, and testing for unexpressed dominant genes, are both means of determining serious health implications for future children and of increasing reproductive choice. Prospective parents who discover they are at risk of having affected children may elect to forego having children, or they may seek assistance through the new reproductive technologies, in order to maximize their chances of having healthy children.

Population-based carrier detection has recently been recommended to be available for cystic fibrosis, a common and serious genetic disorder. Such testing is complex and requires the testing of many mutations in the CF allele. The need for expert genetic counseling by a professional geneticist is essential for providing appropriate genetic information. Carrier testing is routinely carried out in certain ethnic groups in which specific genetic disorders are known to occur with increased frequency and where reliable carrier tests are available. Examples of such testing are those for Tay-Sachs disease, Gaucher disease, sickle cell anemia, and the thalasssemias, all of which are characterized by a distinctive ethnic distributions.

C.Multigenic traits and diseases

Multigenic traits, as the name suggests, are the product of more than one gene. Because multigenic traits are influenced by the combined action of several or perhaps many genes, a continuum of phenotypes commonly results. Body weight and

cholesterol levels are examples of common multigenic traits that clearly illustrate the wide variability that occurs among populations. Most multigenic traits are also multifactorial which means that the trait has both a genetic and an environmental component.

Complex diseases, a particular type of multigenic and multifactorial traits, are increasingly the subjects of genetic research. These diseases are "complex" because they are often influenced by gene-environment interactions, gene-gene interactions and other confounders. Various genetic approaches are used to elucidate the biological interactions and pathways of complex diseases. For some diseases, exploratory research is finding genes and gene products that may be potential therapeutic targets, or diagnostic markers, or both. These studies are in progress in the context of clinical and preclinical research. Alternatively, other clinical studies seek to confirm relationships between specific alleles and diseases, with the goal of developing treatment modalities.

Understanding the genetics of complex diseases such as Alzheimer's disease, asthma, or cardiovascular disease is challenging because of a host of variables that affect susceptibility, onset, course, and treatment. Potential applications of ongoing genetic research related to complex diseases include:

1. *predictive testing* to determine an individual's likelihood of exhibiting a disease;
2. *diagnostic testing* to confirm whether an individual has a disease; and
3. *prognostic testing* to predict the likely course of the disease in an individual.

One method of making *genotype-phenotype correlations* in complex diseases is through *association* studies. Association studies involve comparing the frequency of alleles at a particular locus in individuals with a disease and in individuals without the disease. The alleles and disease are "in association" when the differences in allele frequencies between the disease and non-disease populations are statistically significant. Association studies often involve the case-control design comparing cases of affected individuals with well matched, unrelated, unaffected controls. New technology to navigate the human genome such as haplotype and single nucleotide polymorphisms (SNPs) mapping is expanding the applications of association studies. For example, association studies may yield a pattern of DNA markers associated with a particular disease or other phenotypic trait.

Another type of multigenic trait that is frequently the subject of research involves the genetic basis for responsiveness to medicines. *Pharmacogenetics* is commonly defined as the study of inherited genetic variations that influence responsiveness to medicines in terms of safety and efficacy.[3] Pharmacogenetics is not a new science. Some of its

[3] The terms "pharmacogenetics" and "pharmacogenomics" are often used interchangeably. While there are no universally accepted definitions, "pharmacogenomics" is typically interpreted broadly to encompass the genome, as in gene-gene interactions, and its products, such as RNA and proteins, that influence responsiveness to medicines.

applications, including, for example, the effect of genetic variations on drug metabolizing enzymes, have been recognized for decades. However, the applications of pharmacogenetics research are expanding as our knowledge of the many variables that affect responsiveness to medicines increases.

A typical pharmacogenetic study might be conducted in conjunction with a clinical trial of a drug. Extensive data are collected on the safety and efficacy of the drug in trial volunteers. These data are then compared with genetic data from the trial participants for the purpose of identifying genes, DNA markers, or patterns of markers that correlate with particular drug responses, such as good efficacy or safety, or lack of efficacy, or susceptibility to side effects.

A. Applied research and development

Much genetic research seeks basic information that has no immediate application to the diagnosis or treatment of genetic disease. On the other hand, if basic research generates information that has clinical implications, the complicated challenge for IRBs is determining when research information is of meaningful clinical value.

In single gene disorders, correlation of mutations and phenotype is often relatively easy and often offers immediate benefits to research subjects. Some loci, however, including the gene for cystic fibrosis, house a plethora of alleles, with a wide spectrum of expression and bewildering implications for health or for mild to serious disease. Thus, even in a seemingly simple genetic model of disease, determining the clinical meaning of an individual's genotype can be difficult.

As genetic approaches are applied to complex common diseases, such as asthma, type II diabetes, and high blood pressure, the transition from research data to provisional results to clinically valid genetic information will be even more difficult. Large trials and replication studies will be necessary for valid conclusions and applications in clinical care.

The blurring of lines between research and clinical care pose special challenges to IRBs. IRBs should evaluate (1) the investigator's plan for assessing the validity of research results, (2) when and how investigational test results will be reported to subjects, and (3) how the transitional results will be explained to the subjects, both during the informed consent process and at the time the results are reported. If the results will be used for clinical decision-making, the laboratory reporting the results must be CLIA certified.

B. Newborn screening

Testing newborn infants to detect serious genetic diseases has become routine medical practice. Phenylketonuria (PKU) is one of the serious genetic disorders that can be

reliably detected in the newborn period. Affected infants, when identified and treated with a special diet, are spared most of the serious effects of the disease, including mental retardation. All 50 states currently screen newborn infants for PKU, and newborn screening protocols are expanding rapidly. Some states now screen for up to 30 or more disorders, including those with clearly effective remedies and some whose treatments and outcomes are considerably less certain. Because virtually all infants are available for testing in the newborn period, some investigators and laboratories have suggested that newborn testing might be added for disorders for which treatment is not yet available, but for which treatment is likely to be available in the foreseeable future.

Newborn screening is mandated by law in most states, with little or no provisions for obtaining parental consent before testing the infant. The justification for this approach is that the benefits of testing to both the infant and to society far outweigh the invasion of privacy and personal autonomy. The advent of very powerful screening technologies, however, for simultaneous, rapid, and accurate testing for hundreds of genotypes has generated debate about revising protocols to include parental consent for determining genotypes for as yet untreatable disorders. A national Newborn Screening Expert Panel is currently reviewing those diseases considered for screening, for which excellent treatments are available, and for which permission for screening might not be necessary. The issue of requiring informed consent for screening for as yet untreatable diseases remains unsettled at present.

F. Bioinformatics and data sharing

Electronic record keeping and database archiving is playing an increasingly important role in human genetics research. Such databases may be broadly configured in three ways: local use only, limited shared use, and open access. Local access may consist of databases residing on local servers accessed only by one or more local computers. Such databases often contain identifiers, including names and patient identification numbers. Moreover, such databases may also contain pedigree and phenotype information, as well as genotypes. Security of these servers should therefore be maximal, particularly if they are connected to the internet, as is usual. In particular, independent firewalls may be required internal to the institutional firewalls. Further, at some institutions, the information technology service has remote access to all computers and servers. As this is often unknown to the local users, it poses a substantial problem in confidentiality. IRBs should evaluate provisions for confidentiality and assure appropriate safeguards for personally identifiable information.

Some datasets containing human genetic data may be openly available over the internet. For example, many journals now require the electronic archiving of raw genotype data or expression array data as a condition of publication. Frequently, such datasets reside on the servers of the journal or the publisher, no longer under the authors' supervision. Such datasets should be scrutinized and cleansed of any identifying information, including initials of names and other patient information. Inclusion of pedigree information is of particular concern because sex and birth order

may provide sufficient information for identification. Alteration of such data by changing birth order or adding false siblings is sometimes advocated as a means of filtering out identifying information. However, because such data alteration may limit usefulness of the data for replication studies, readers should be alerted to these devices. Indeed, some IRBs require such stringent measures to mask identification that the conclusions of the publications cannot be readily replicated by others using the archived data. In the continuing absence of a solution to this dilemma, investigators, editors, and the IRB may be required to negotiate an acceptable approach. Anticipating this issue when first seeking IRB approval is prudent since patient identification must be sufficiently protected while still maintaining the longtime scientific practice of allowing study replication. Additionally, NIH now plans to require prospective plans for sharing of data as a new component of grant applications, and will consider plans for adequacy of sharing as a criterion for application review. The extent to which this implies that databases developed with NIH support must be generally available for secondary "data mining" remains to be established.

Two further issues with open datasets, or even closed foreign datasets open to a U.S. investigator, are the manner in which the patient samples were ascertained and the content of provisions for informed consent. One might assume such a "secondary" user of data stripped of identifiers would be not held accountable for the exact ascertainment, but this issue is unclear and warrants further discussion.

G. Genetic counseling and psychosocial issues

In recent years genetic counseling has matured into an integral part of medical genetics and genetics research. The amount of new information about genetics has increased exponentially, and much of this information is applicable in the lives of individuals who are dealing with medical problems or who are participating as subjects in genetics research. The profession of genetic counseling has expanded to deal with burgeoning knowledge and to provide appropriate benefits for patients and clients. Specialized genetic counseling programs are offered at a host of universities, and counselors are now professionals certified by the American Board of Genetic Counseling. In addition to professionally certified counselors, individuals in other ancillary professions are valuable contributors to the counseling and education process. These persons include clinic coordinators, nurses, social workers, and others, who are adequately trained and knowledgeable in genetics and are proficient in communication skills.

The role of counseling is to assist patients and clients in understanding the genetic dilemmas that bring them to genetics clinics and genetics research. Counselors discuss scientific and mathematical aspects of genetics as well as a host of psychosocial issues that arise in families who are coping with their own genetic legacies. When individuals are considering becoming subjects in genetics research projects, counselors may play a pivotal role in delineating what can be reasonably expected from their participation. A major issue is helping prospective subjects understand the *"therapeutic gap,"* or the lag time between what is learned from pure research and the realization of treatment

modalities for genetic disorders: subjects should understand that treatment for genetic diseases may be developed only much further in the future. A second major topic for counseling and discussion is the psychological phenomenon of *"survivor guilt"* that sometimes develops when individuals learn that they may indeed survive other relatives who have a devastating, even lethal, genetic disease. Finally, a third critical issue is *"parental guilt,"* a common response when serious, often fatal, diseases affect children and profoundly affect family planning in the immediate and extended family. Genetic counseling protocols should allow time for thorough discussions of these issues and any other concerns of both subjects and investigators who are embarking on a genetics research project.

The necessity of genetic counseling and education will depend on the design of the proposed research and the needs of the proposed subjects. IRBs should determine whether genetic counseling and education should be provided as an integral part of a research protocol.

H. Children and adolescents

The interests of children and adolescents in genetics and genetics research have been the focus of intense concern for many years. Genetic testing and genetic information can have profound implications in the lives of patients and subjects. Information about deleterious genes can be discouraging and depressing. Information that is conveyed carelessly can affect the individual's sense of self-worth and sense of future prospects. Whether and how genetic information should be conveyed to children or adolescents are issues that go to the heart of the family and the role of the parents in managing their own lives and those of their children. Depending on the constellation of circumstances in the family, parents may seek genetic testing for themselves and their children. They may plan to disclose genetic information to their children or not. Above all, they must understand that insensitive disclosure and mismanagement of genetic information can have a seriously negative impact on their children.

The professional genetics community supports a consensus that genetic testing in children is appropriate if the child stands to enjoy an immediate medical benefit as a result of the testing. Testing children for genes that cause childhood- or adolescent-onset cancers, for example, permits cautious medical monitoring of children who are found to be at risk and precludes such monitoring for those who are not at risk. In the absence of an immediate medical benefit, however, geneticists urge caution in counseling parents thoroughly about both the positive and negative aspects of generating genetic information on children. Once this counseling is complete and the geneticist is satisfied with the understanding and motives of the parents, the geneticist should defer to the parents as the appropriate decision makers for their own families. This latter approach does not, however, represent a consensus among geneticists, and there are many professionals who assert that no children should ever be the subjects of genetic testing in the absence of an immediate medical benefit.

In the absence of consensus on research and testing in children and adolescents, IRBs should evaluate each proposal individually and provide protections for minors as appropriate.

C. Collection of race and ethnicity data

The Human Genome Project has resulted in a wealth on information about the genetic constitution of mankind. One of the most valuable results of this project has been the confirmation that all human beings share a vast amount of genetic information in common. What differences we do observe, or perceive, among humans are confined to about one percent of our genetic material.

This new information is contributing to an on-going debate about classifications of race and ethnicity across the human population. The current prevailing view that race often has a social rather than biological basis is prompting questions about the continued use of racial classifications in medical research and clinical medicine. However, population differences in disease prevalence do exist, and the extent to which these differences can be explained by genetic components, as well as environmental or socioeconomic factors, is a topic of great interest and import. Additionally, in an effort to address health and healthcare disparities, federal research and oversight agencies currently require the collection of race and ethnicity data. This requirement allows the agencies to monitor and promote the inclusion of women and minorities in clinical research and fair access to the benefits of research, and to advance knowledge of gender and group differences in health and disease susceptibility.

Exploring genetic variation among populations and associating the variation with disease may speed the discovery of disease related gene mutations and advance understanding of the role of genes in disease and the differences in the prevalence of disease across populations. Defining genetic characteristics of human groups may also facilitate the tailoring of gene-based pharmaceuticals to the unique genes of individual groups, and ultimately to the unique genotypes of individuals. The results of this research, however, have the potential to stigmatize groups and to perpetuate biological concepts of race.

As the boundaries of biological race become less distinct, research proposals that include an element of race must offer a scientific justification for this approach. IRBs should carefully review research proposals that involve collection and analysis of population data to be sure the study hypothesis is justified, the design of the study is statistically valid, and that potential harms to named populations are considered and minimized. Similarly, distinctions based on ethnicity should be well justified when ethnically defined groups are the source of subjects for specific research projects. Defining genetic characteristics of human groups may, however, facilitate the tailoring of gene-based pharmaceuticals to the unique genes of individual human groups, and ultimately to the unique genotypes of human individuals.

J. Subject access to data

Data generated in the course of a genetics research project are *interim findings, or provisional results*. These data are subject to replication and confirmation before they are regarded as reliable diagnostic information. Further, many of the very rare "orphan diseases" are studied in only one or a few university research laboratories that are not regulated under the Clinical Laboratory Improvement Act of 1967, and as subsequently amended, and are therefore restrained from disclosing research and testing results. Because of these uncertainties and legal restrictions, investigators are usually reluctant to disclose this information to research subjects.

While subjects are presently denied access to interim data, discussions among investigators and subjects in genetics research have raised valid questions about the interest of subjects in some provisional laboratory findings. If, for example, a study identifies some persons as possibly at high risk for an allele associated with a particular cancer, those persons might elect to pursue further testing sooner rather than later if they are informed of the provisional result. This possibility should be included in genetic counseling and discussed with the subject as part of the consent process, with the decisions resting with the research subject. The critical caveat is that the subject must understand the provisional nature of the data and the experimental uncertainty of unconfirmed research results.

On the other hand, research subjects also have a *right not to know* information about themselves that is generated in genetics research. They may be concerned about the possibility of psychosocial harm in receiving new information, or in learning about inevitable future disease, or in dealing with survivor guilt. Thus, the right to decline knowledge of research results should also be presented to the subject as an option in the consent process.

A third dilemma may arise when a study yields *incidental results* about a research subject. While such results may not have been anticipated in the original experimental design or in the consent protocol, the new information could be of significant interest to the research subject. The possibility of this kind of event, even a remote possibility, should therefore be addressed in the consent process.

K. Management and secondary use of tissue samples

Possession and ownership of tissue samples has come under close scrutiny in recent years because of evolving questions about on-going use of archived samples. Historically, any interests of individuals in their tissue samples have been severed, either by law or by custom, at the time the samples were removed from the body. These samples have come into both the possession and the ownership of the laboratory or institution where they were acquired and stored and have contributed to vast archives

that are immensely valuable in large population studies involving multiple collections housed in diverse institutions.

With the advent of protections for human subjects, however, the elements of ownership have been bifurcated, with interests vesting in both the investigators and institutions, on the one hand, and in the subjects, on the other hand. The legal concept of ownership is divided into three elements: the right of possession of a thing, the right of enjoyment (of the products) of a thing, and the right of disposing of a thing. Historically, all three elements vested in the institution that collected tissue samples. More recently, however, human subjects have been vested, in some situations and under relevant provisions for informed consent, with the right to have their samples destroyed if they decide to withdraw from a study. Thus, the element of possession rests with the institution, subject to the subject's right to disposing of the sample. The element of enjoyment arguably rests with both parties: investigators and institutions may enjoy the benefits of using the samples in their own research, while individual subjects may enjoy the benefits of knowledge generated about their own health prospects.

One current dilemma derives from enjoyment of commercial gains from products of research by investigators and institutions, to the intentional exclusion of subjects from these benefits. This issue has already been the subject of civil litigation, and it remains unsettled.

Research in human genetics now presents *special problems* that IRBs should consider. The rapid expansion of information and knowledge of genetics has implications for feed-back to individual subjects – information that is relevant to their health and welfare or to the health and welfare of relatives, information that was not foreseeable or anticipated when tissues were originally collected. The conditions for maintaining privacy and confidentiality, while still respecting the welfare of subjects, should be carefully assessed by IRBs by considering these unforeseen possibilities when evaluating original protocols.

Because archived samples may well be used by investigators at least one level removed from the donor subject, the IRB should assure that appropriate approvals and consent existed for the originating research. How the investigator and IRB deal with the secondary use of data or repository tissue will vary depending on how, where, and when stored material is archived. If the research is based on tissue archived at a single institution or organization and the investigator is a part of the institution, the institutional IRB knows the conditions for the storage and use of the materials and the investigator is subject to the same IRB for review and approval of the proposed research use. If the tissue is archived as part of a consortium when the materials are kept at a central site serving the multicenter institutions involved in the initial collection of the materials, the consortium institutions should anticipate by prior arrangement the management and use of the materials stored as part of the study, and the mechanisms for obtaining IRB review and supervision. If the tissue repositories are constituted from multiple sites, investigations, and investigators as a resource for secondary use by investigators not

necessarily associated with the collection of the materials, the responsible agents of the repository of the tissues should have established policies and procedures for how the materials and information are stored, how approval for their use should be obtained, and how the responsibility for IRB oversight will be determined.

Therefore, an investigator seeking review and approval from the responsible IRB should provide information that specifies the characteristics of the repository. The pertinent information should include: (1) how, where, and why the original clinical tissue was collected; (2) whether the collection was approved by an appropriate IRB; (3) if the original consent covered secondary use; (4) the conditions established by the repository for release of materials and the extent of removal or destruction of identifiers (5) any limitation on the secondary use of the materials; (6) requirements for feed-back to the original human subjects when the materials have not been stripped of identifiers; and (7) whether a certificate of confidentiality has been obtained.

Another critical issue related to maximizing privacy and confidentiality is the question of *consent for future use* of tissue samples and maintaining or removing identifying information or codes on archived tissue samples. If no identifiers are attached to tissue samples, the concerns of the IRB are minimal. However, if identifiers are attached, or may be attached or removed, the IRB should consider the source of authority for attaching, or removing, or destroying this information. In human genetics research, removal of identifiers may not be in the best interests of the subject because newly derived genetic information may be of great significance in the life of the subject. For this reason, then, the subject should be the authority for maintaining, or removing, or destroying identifying information. If the subject elects to retain identifiers for the purpose of receiving future information, the subject and investigator should establish a reciprocal responsibility for keeping the investigator informed about how to contact the subject, so that the investigator can contact the subject quickly and accurately. The subject should be informed about these options, and the consequences of these options, in the consent process, so that feed-back of important new information can be facilitated to those who elect to receive such information.

For those subjects who elect to retain identifying information for the purpose of receiving future genetic information, the IRB should consider the most optimal methods for protecting privacy and confidentiality. Potential subjects should be fully informed of the limits of confidentiality for the specific original protocol, and how confidentiality will be maintained if the archived tissue sample is used in the future.

Tissue bank samples that already exist, such as archived newborn screening samples, present a different problem for management by investigators and IRBs. Prior consent for future use may not exist, may never have been obtained, or may have been too vague to be useful. Predicting future use may not be possible. IRBs should consider appropriate measures to allow such research within ethical and legal guidelines. Institutions involved in genetic research should have policies and procedures that address these special issues and provide training for the IRBs and investigators responsible for protecting the human subjects in such research.

IRBs should consider the issues outlined above in view of existing and emerging federal regulations, including CLIA and HIPAA.

IV. Expedited Review and Exemption from Review

The expedited review process is available for minimal risk research in which the research activity is limited to one of a specified category, including the collection of blood samples. In genetic studies that involve a blood draw, the additional psychological and socioeconomic risks may raise the risk beyond “minimal” risk. IRBs should carefully evaluate this possibility.

Genetics research that is based on collections of samples from deceased persons, or on transformed cell lines, or on samples from which all identifiers have been eliminated, is eligible for expedited review. Even in expedited review, the IRB should consider provisions for consent for future use of surplus tissue samples.

Genetics research entails the gathering of family history information that may be identifying. Such research does not qualify for exemption from review under federal regulations. [Federal Policy § ___.101(b)(2)]

V. Applicable Laws and Regulations

Protection of Human Subjects, 45 C.F.R. 46 (1991).

For access to federal legislation and regulations, go to

http://www.access.gpo.gov

VI. Relevant Publications

ASHG/ACMG Report. Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Am J. Hum Genet 57:1233-1241 (1995).

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Pelias, MZ. Federal regulations and the future of research in human and medical genetics. J. Continuing Education in the Health Professions, 21:238-246 (2001).

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Rothstein, MA, Epps, PG. Pharmacogenomics and the (ir)relevance of race. The Pharmacogenomics Journal 1: 104-108 (2001).

Schwartz, RS. Racial profiling in medical research. N Engl J Med 344 (no.18): 1392-1393 (2001).

Shriver MD, Smith MW, Jin L, Marcini A, Akey JM, Deka R, Ferrell RE. Ethnic-affiliation estimation by use of population-specific DNA markers. Am J Hum Genet 60:957-964 (1997).

Supplemental Brochure for Population-Based Research involving Genetics: “Informed Consent: Taking Part in Population-Based Genetic Research”, http://www.cdc.gov/genetics/info/reports/policy/brochure.htm (visited11/16/2001).

Wood, AJJ. Racial differences in the response to drugs – pointers to genetic differences. N Engl J Med 344 (non. 18): 1393-1396 (2001).

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