Committee 2
Genetic Knowledge, Human Values
and Human Responbility

DRAFT--7/1/95
For Conference Distribution Only

THE PRESENT STATE OF GENETIC KNOWLEDGE AND ITS IMPLICATIONS FOR GENETIC SCREENING

by

Verle E. Headings
Professor of Pediatrics, Genetics and Human Genetics
Howard University
Washington, D.C., USA

The Twentieth International Conference on the Unity of the Sciences
Seoul, Korea August 21-26, 1995

ABSTRACT

A hallmark of genetic screening is the diversity of strategies employed toward the common goal of ameliorating or preventing inherited disorders. The state of technology for intervening in a given disorder and the state of screening technology dictates the screening strategies. The latter can be classified roughly by stages of the life cycle -- presymptomatic late onset disorders among adults, reproductive age population for heterozygote states, presymptomatic disorders among newborn infants, the fetus, the 8-cell zygote, and gametes. These are further classified as to high risk family based screening, high risk population based screening, and universal screening in a stage-of-life cohort.

The introduction of DNA-based characterization of gene loci, identification of specific mutants, and technologies for cost effective screening in families and populations at this level offers the prospect for a substantial expansion of genetic screening, thus enhancing the exercise of more effective choice to prevent devastating disease in self or family. However, the discovery of extensive genetic heterogeneity within and among gene loci for many disease phenotypes, the range of potential psychosocial burden accompanying screening for certain diseases, and the limited and less than ideal present options for intervention in many disorders requires a careful balancing of benefits and burdens when making choices regarding screening. This calls for the joining of efforts from professionals in the molecular sciences, psychosocial sciences, ethics, and clinical

sciences toward a common goal of enabling individuals to prevent genetic disorders in their own families. One important avenue to prevention begins with genetic screening.

INTRODUCTION

The present knowledge of human gene structure, the mechanisms for gene expressions in phenotypes, the diversity of mutations within a gene which points to differing genotype-phenotype correlations, and the complex multifactorial nature of some phenotypes all contribute toward defining diverse genetic screening strategies. In this work I will first set out the relationships between these fields of genetic knowledge and the diverse screening objectives and strategies which are now in practice or under consideration. In the second part I will identify both benefits and potential burdens inherent in various objectives and strategies, and illustrate these with cardinal examples of inherited disorders.

SCREENING STRATEGIES AND OBJECTIVES

As a means for circumscribing the genetic knowledge which bears significantly on genetic screening as practiced or under consideration let us first examine screening strategies and objectives (Table 1). The first item of note is that the spectrum of strategies spans much of the life cycle. The specific stage at which screening is offered is governed by the state of screening technology, the most realistic objective for disease prevention, and preferences of persons at risk for a given disorder.

Presymptomatic disease screening for late onset genetic disorders is adapted to the fact that many phenotypes first express months or years after birth. These could be illustrated by familial adenomatous polyposis which with near certainty develops into colorectal cancer (Powell, 1993), breast cancer (King, 1993), Huntington Disease (Benjamin, 1994), specific hyperlipidemias (Sandholzer, 1992), apolipoproteinemias (Wilcken, 1993), (specific locus diseases); and hypertension, hypercholesterolemia, and diabetes mellitus (multifactorial diseases). The objectives and strategies here are diverse depending on the state of the art in interventions. Early detection of cancers by screening at-risk populations, in principle, allows effective surgical removal before metastasis occurs. Identifying the presence of the Huntington Disease gene early in life offers opportunity to devise a more realistic life plan, including informed reproductive planning, given the one-in-two chance of transmitting the gene to offspring. Screening for specific lipid related disorders prior to occurrence of stroke or myocardial infarcts offers opportunity to diminish blood levels of the offending lipids by pharmacologic treatment. Screening for hypertension, hypercholesterolemia not of single gene origin, and diabetes mellitus allows for minimizing morbidity by both dietary modifications and other life style changes as well as pharmacologic treatments.

Screening the reproductive age population for heterozygote states is well illustrated by Tay Sachs disease, sickle cell disease and beta-thalassemia; the intent being to provide important information for reproductive planning by individuals in a carrier-by-carrier mating (Motulsky, 1994). Indeed, this strategy has been particularly effective in reducing the incidence of Tay Sachs disease and thalassemia in some populations.

Universal newborn presymptomatic disease screening occurs in every state in the United States by legislative mandate, as illustrated in a recent listing of screening practice in various jurisdictions (Table 2), and in many countries. However, these fixed package screening protocols for each state jurisdiction do not optimally take account of each infant's risk for genetic disease. Thus, a strategy for devising individually tailored screening protocols has been proposed (Headings, 1988; Sherman, 1989). This newborn stage-of-life strategy is driven by the fact that a relatively narrow window of time is presented following birth for which there is available effective prevention of all or part of the expected phenotypic morbidity.

Screening the fetus for genetic disease is organized around two strategies. Single gene locus disorders or chromosome anomalies in high risk matings can be screened for during the first trimester through sampling of chorionic villi, or during the second trimester through sampling of cells in the amniotic

fluid. A promising technology currently being investigated is screening for these disorders in rare fetal cells which can be obtained from maternal blood circulation. In fetuses at substantial risk for major malformations the latter can also be screened for by ultrasonography. In each instance the goal is to offer an option of selectively terminating a pregnancy or conversely to realistically anticipate the birth of a 'special needs' infant. The second strategy is universal prenatal screening (in principle all pregnancies) for certain chromosomal trisomies and neural tube closure defects (multifactorial malformation). For both of these screening entails assaying the pregnant woman's plasma for alpha fetoprotein, and other substances (Macri, 1992).

Screening the 8-cell zygote in vitro for genetic disease following in vitro fertilization is a strategy appropriate for the mating which is at high risk for a specific Mendelian disorder, allowing an option of zygote selection.

Gamete screening is presently available in some centers in the form of sperm sorting, thus allowing selective fertilization of the ovum with X or Y bearing sperm.

SCREENING TECHNIQUES

The fact of there being a large number and types of screening strategies and objectives indeed highlights the complexity of genetic screening as a paradigm for intervention in human disorders. This complexity is further amplified by diverse screening techniques, which roughly can be classified as gene

product screening, correlated metabolic product/marker screening, and DNA based screening. Examples of these are noted in Table 3. We shall examine characteristics of several technologies being applied to screening.

DNA based screening itself presents considerable technique diversity. As gene structure, organization and mutants have been progressively clarified it becomes evident that screening at the level of a gene by use of DNA probes in some instances encounters special problems not encountered when screening a gene product or a correlated biochemical marker. To illustrate such a problem let us note that screening for phenylketonuria by the Guthrie microbial inhibition assay quantifies plasma or urine phenylalanine, a metabolic product which accumulates as a consequence of a failed gene product, usually phenylalanine hydroxylase. Assaying such a secondary but functionally significant molecule in only a quantitative dimension allows us to circumvent identifying specific mutants,in the phenylalanine hydroxylase gene, of which over 200 different ones have been identified (Ramus, 1995). On the other hand employing allele specific oligonucleotide (ASO) probes allows for quick and efficient screening for specific mutants within a gene, and may permit more definitive projection of disease and prognosis, based on any established genotype-phenotype correlations. Such correlations are likely to be increasingly valuable diagnostically, as for example with the CFTR gene locus in which mutations yield a spectrum of cystic fibrosis (Tsui, 1992; The

Cystic Fibrosis Genotype - Phenotype Consortium, 1993), congenital bilateral absence of the vas deferens (Pignatti, 1994), and some cases of disseminated bronchiectasis (Pignatti, 1995). However, with numerous mutants at a locus in the population, as for example with the CFTR locus where more than 400 different mutants have already been identified, there is presented the costly proposition of screening with multiple ASO probes. Fortunately, technologies are being developed which can detect multiple specific mutants simultaneously, such as by multiplex polymerase chain reaction (PCR) amplification of various segments of the CFTR gene, followed by multiplex allele-specific oligonucleotide probe ligation assays (Eggerding, 1995). Automation of this process and high volume through-put for a given laboratory may allow screening for multiple mutants to become cost effective.

A growing list of neuropsychiatric disorders, numbering at least eight (Mandel, 1994; Kawaguchi, 1994) exhibit an unstable expanded trinucleotide repeat in a given gene locus. This is now the basis for molecular diagnosis of these disorders. Intergene-rational changes in repeat number occur, together with associated changes in probability of phenotype expression in offspring, which introduces a measure of unpredictability into genetic counseling. The direction and magnitude of change to be expected in offspring is presently difficult to predict. Huntington Disease as one of these trinucleotide diseases is shown to be a consequence of the trinucleotide expansion, even though the

mechanism by which it causes death of neurons is not yet known (Kremer, 1994; Goldberg, 1994). Recent demonstration of variable degree of repeat number mosaicism among sperm of males who transmit Huntington Disease may provide one avenue for predicting age of onset (severity) in offspring (Telenius, 1995).

Recently introduced technologies offer more generic DNA screening strategies which identify any and all mutants in a given gene locus. These are based on differences in mobility between single stranded wild type and mutant DNA sequences in polyacrylamide gels (single-stranded conformation polymorphism method) (Orita, 1989; Sarker, 1992); chemical or enzymatic cleavage of heteroduplexes formed between complementary mutant and wild type DNA sequences (Cotton, 1988; Lishanske, 1994), and differences in denaturation between mutant and wild type double-stranded DNA sequences as detected by denaturing gels (Sheffield, 1989).

These methods have been applied to screening for mutants in genes such as the dystrophin gene (Prior, 1994), the cystic fibrosis gene (Highsmith, 1993; Ravnic-Glavoc, 1994), and the p53 gene in which mutants are responsible for certain tumors (Soto, 1992; Tsongalis, 1994). Furthermore, it is noteworthy that these technologies appear to lend themselves to screening for both homozygote and heterozygote genotypes involving a mutant.

Universal prenatal screening for open neural tube closure defects (NTDs) (anencephaly, encephalocele, meningomyelocele) and for chromosome trisomies such as in Down Syndrome (DS) are

accomplished by assaying maternal serum levels of alpha fetoprotein. This protein, normally present in the liver of the fetus, diffuses into amniotic fluid and blood of the mother. Levels in these fluids increase when the fetus has a NTD and decrease when it has DS. Both the specificity and sensitivity of the test are limited (Macri, 1986) but the accuracy of the screen outcome can be significantly improved by concurrently assaying one or two additional chemicals in maternal blood (Macri, 1992). The existence of a 95% false positive rate in the screen test for NTD's requires a costly and time consuming protocol of followup testing for all screen positives. Until a false positive test is clarified there is considerable anxiety for the parents (Burton, 1985). This highlights the fact that screening techniques with relatively low specificity and sensitivity may have utility but can yield adverse consequences.

GENETIC KNOWLEDGE AND GENETIC CHOICE - BENEFITS AND BURDENS

Genetic screening may be perceived as enhancing the exercise of more effective choice to prevent devastating disease in self or family. Such a goal is in the spirit of choosing autonomously, without internal or external encumbrance (Gauthier, 1993). The strategies reviewed earlier each in its own way provides information at a stage of the life cycle which permits certain members of a family to intervene in the natural history of a disorder. However, this emphasis on prevention through screening risks labeling the bearers of undesirable genes as somehow less desirable members of society. The parent who is

parenting a genetically handicapped child is confronted with twin tasks which appear to entail conflicting goals. Investing heavily in the development of a 'special needs' child while also making decisions to submit to any of several prenatal screening strategies in order to avoid recurrence of the handicap in future children can create strain for the parent. The risks of disinvesting in the handicapped child or, at the other extreme, experiencing a guilt driven over-investment and parenting burn-out are real potential consequences of an emphasis on prevention through genetic screening in this context.

Social stigmas which accompany genetic disorders are an acknowledged aspect of various disorders. Historically one can decipher a 'quarantine mentality' which appears to propel elements of societies toward separating themselves from persons labeled as bearers of an inherited disease (Markel, 1992). This is dramatically illustrated in families where Huntington Disease, a progressively dementing neurodegenerative disorder, is present. The experience of many such families is that social linkages diminish after a diagnosis is confirmed, leading to social isolation of the family.

The relationship of this latter example to presymptomatic predictive screening introduces several psychosocial and ethical concerns (Chapman, 1990; Huggins, 1990). A screen positive yet healthy member of a family acquires stigma in advance of its usual timing in the natural history of the disorder. Predictive screening using linked DNA restriction fragment markers requires

the cooperation of family members in the testing, who may not wish information on their gene carrier status. Thus, we may properly conclude that it is a family rather than an individual who is a patient in genetic screening (Wertz, 1989). The principles of individual autonomy, confidentiality and privacy are under challenge in circumstances such as this. A majority of molecular genetic disease diagnoses currently utilize linked markers and thus present some version of this ethical challenge (Nolan, 1988). Such potential family-based conflicts may with time be somewhat ameliorated as increasingly probes for specific gene mutants rather than for linked markers are employed (Benjamin, 1994). This evolution in molecular screening technology in an interesting manner qualifies as an instance of applied preventive ethics, a relatively recent interest in anticipating and minimizing ethical conflicts in health care choices (Parker, 1994; Forrow, In press)

Limitations imposed on genetic screening by the state of genetic knowledge becomes increasingly evident as molecular characterization of genes and mutations progresses. Gene interactions and gene-environment interactions appear to alter the disease severity, the type of tissue in which expressed, or age of expression of an identical mutation among individuals. Thus, screening for a given mutant does not with certainty lead to prediction of clinical phenotype (Romeo, 1994; Motulsky, 1994). This has been well illustrated recently for untreated phenylketonuria (Ramus, 1995).

A limitation of testing/screening for heritable variation in DNA is that this is focused on information which is most resistant to disease intervention strategies. On the other hand, measurment/screening for an outcome variable, as for example blood cholesterol level, commonly reflects multiple causal factors, including environmental variables. Thus, such a screened variable may be more accessable to direct intervention (Durfy, 1993). However, a contrasting current example of screening for an outcome variable is identifying the pre-diabetic state by an abnormal glucose tolerance test (GTT). The dis-advantage of this approach is that by the stage of an abnormal GTT approximately 80% of pancreatic islet cells may be destroyed. Current multi-center studies focusing on a genome-wide search for microsattelite DNA markers for diabetes mellitus, if successful, might lead to a strategy of earlier stage risk detection prior to the expression of a phenotypic outcome variable, when intervention might prevent extensive islet cell destruction.

Two types of genetic heterogeneity introduce further complexity. Mutations at two or more loci at times produce a similar clinical phenotype. Thus, any DNA-based screening must cope with this fact. Alternatively, some phenotypes may be the consequence of numerous alternative mutants in a single gene locus; e.g. more than 400 different mutations have been reported in the gene locus responsible for cystic fibrosis (Tsui, 1992). This poses two considerations for the practice of screening. 1)

Not all such mutations are functionally equivalent, i.e. there is need to explore genotype-phenotype correlation. 2) Screening by allele specific oligonucleotide probes requires a multiplicity of probes, one for each mutation to be included in the screen. This can represent considerable cost.

Both types of genetic heterogeneity pertain to breast cancer; and yet to be clarified are the penetrance of mutant expression at differing loci and estimates of gene-environment interactions contributing to risk of cancer. (ASHG Ad Hoc Committee on Breast and Ovarian Cancer Screening, 1994). These elements collectively illustrate the complexity of applying DNA-based screening to presymptomatic prediction of a genetic disorder of this type.

The magnitude of false-positive and false-negative screening results must be established for each screening technique. This, together with quality control of testing pose considerable research effort before a given screening can be offered as standard clinical practice (National Advisory Council for Human Genome Research, 1994). Indeed, a much larger set of questions deserve investigation before a new technically validated screening test can be offerred in clinical practice -- how to assure adequately informed consent, maintaining confidentiality of results and limiting discrimination, negative impact on self concept and family dynamics, efficacy of interventions, etc (Baird, 1990). Not only efficacy but quality of intervention deserves scrutiny. A focus on prenatal genetic screening with

its option of terminating a pregnancy presents a highly invasive form of intervention (Lippman, 1991).

Some new predictive genetic screening protocols clearly provide significant benefit for individuals and families as can be illustrated for familial adenomatous polyposis (FAP). Some 50,000 families in the United States could benefit from predictive screening. Given that this type of polyposis with near certainty progresses to colorectal cancer, recommended intervention protocols until recently included recurring sigmoidoscopy examinations after age 11 years in families where members are at known risk of this autosomal dominant disorder. Early prevention entails colectomy. Screening by multiple sigmoidoscopies represents major physical, psychological and financial burden in contrast to the now available sensitive and rapid molecular assay for mutations in the FAP gene (Powell, 1993).

Newborn genetic screening protocols for a variety of disorders have clearly created opportunity for some beneficial medical interventions in the lives of numerous children. Newborn screening is clearly coupled with direct health benefit to the individual screened. However, a recent review of 10-year experience in treating hereditary metabolic diseases suggests only partial success overall. Among 65 diseases treatment completely prevented manifestations in only 12%, partially ameliorated the disease in 57%, and failed to

modify manifestations in 31% (Treacy, 1995). Thus, there is a sobering realization that rapidly evolving knowledge about genetic etiology, molecular and cellular pathogenesis, and genetic screening stategies has not yet been meet with comparable success in treatment. In contrast, certain other screening strategies, e.g. presymptomatic screening for Huntington Disease, Alzheimer Disease, Duchenne Muscular Dystrophy, or prenatal screening for Down Syndrome, currently allow for very limited options for direct intervention in the disorder. The principal benefit of such screening is for more rational planning/coping by family members, and including prevention of the disorder among future offspring.

BALANCING BENEFITS AND BURDENS

Given the diversity of screening strategies, the diversity of presently achievable interventions in diseases identified by screening, and the possible concurrent benefits and burdens from a given screening initiative it is clear that a process of moral deliberation should govern any given genetic screening service. This deserves a scale of treatment which is outside the scope of this present work. However, a signal principle in a moral framework for genetic screening might well be that of securing for parents and prospective parents the opportunity to choose freely, without internal or external encumbrance, to prevent manifestation of inherited diseases in themselves or their offspring (Headings, 1994). The mechanisms for implementing

choices as well as the perceived burdens and benefits of a given screening strategy quite clearly are interpreted differently among parents. The duty of the screening professional is to secure the foundation for an adequately informed decision-maker in order that knowledge of benefits, complexity, and limitations of a given screening strategy all contribute to a genetic screening choice which enhances the well-being of the recipients.

A PROPOSAL FOR THE PRACTICE OF SCREENING AND COUNSELING

Practitioners in a rapidly evolving discipline of medicine must attend to a process by which a standard of care comes to be delineated. In the areas of screening and counseling standards entail an agreed upon accuracy of testing and prediction of disease risk, a biological and/or psychosocial outcome which is on balance beneficial, acceptable cost effectiveness, and adequately informed individual and familial decision-makers (Juengst, 1994). As a given technology is experimentally applied to screening for a given disorder the timing of its readiness for use in specific high risk families may precede the time of its readiness for application to population level screening.

A standard of an adequately informed decision-maker is rooted in the premise that prevention of a genetic disease is a good, provided that the means for achieving this yields net benefit in the judgement of the recipient. In order to satisfy such a standard the genetic clinician must present to clients:

1. The benefits and burdens of a given screening strategy.

2. The practical limitations of a given technology.

3. Clear distinctions between clinically validated technology and research technology.

4. The points at which a given screening strategy and technology generate moral conundrums.

Traditionally, the process by which innovation is adopted into clinical practice and medical education involves thoughtfully designed research and pilot trials, which eventually may warrant convening of broadly based consensus conferences. In this way a standard of care must evolve from a process of empiric testing rather than by creation of rules of practice developed by self-appointed members of a specialty.

The complexities, limitations, and potential burdens of genetic screening point toward the value of multidisciplinary insights for evolving a standard of care in screening and counseling. The developer of a given screening technology may not always be the appropriate individual to evaluate its utility in clinical practice or the harms and benefits as perceived by recipients. Molecular sciences, psychosocial sciences, ethics and clinical sciences must be applied in a concerted manner toward a common goal of providing options by which individuals may choose to prevent given genetic disorders in their own families.

Public education on genetic screening and disease interventions is at risk of being subverted by excessively

optimistic projections about benefits to be anticipated from a given line of research. This through the collaborative efforts of the scientist desiring recognition and continued funding, and the journalist seeking a 'break through' story for the public. An informed public must be provided insights on moral and practical ambiguities posed by some potential screening strategies. Otherwise some individuals seek inappropriate genetic screening, or conversely become paranoid regarding genetic screening and therapeutic interventions.

As with all endeavors the genetic professional must bring integrity to how she/he translates the raw facts of the science into interpreted facts for the non-scientist. The exercise of such moral obligation can be most reasonably anticipated when the graduate education of scientists includes courses and seminars on ethics, and when there emerges a more ethically attuned culture of science 'at the research bench'.

TABLE 1. GENETIC SCREENING STRATEGIES AND OBJECTIVES

Strategy	Objective
Delayed onset presymptomatic disease screening • in high risk families • in general population • specific gene locus disease • multifactorial disease	Life planning Reproductive planning Ameliorate expression of a phenotype
Adult carrier screening	Reproductive planning
Newborn presymptomatic disease screening • universal • individually tailored • specific gene locus disease	Ameliorate expression of a phenotype
Screening the fetus for disease • specific gene locus • chromosomal disease • malformations - multifactorial	Option of fetal selection Ameliorate expression of a phenotype Prepare for a special needs child
Screening the 8-cell zygote <u>in vitro</u> for disease	Option of zygote selection
Gamete screening	Selective fertilization

Table 2. Disorders for Which Newborns Were Screened in the U.S. (1991)

State/Territory	Hyperphenyl-alaninemia	Classical Galactosemia	Hypo-thyroidism	Maple Syrup Urine Disease	Homo-cystinuria	Biotin-idase	Cystic Fibrosis	Congenital Adrenal Hyperplasia	Tyro-sinemia	Toxo-plasmosis	Hemo-globinopathy
1 Alabama	R		R								R
2 Alaska	R	R	R	V	V	R		R	V		
3 Arizona	R	R	R	R	R	R					R
4 Arkansas	R		R								R
5 California	R	R	R								R
6 Colorado	R	R	R	R	R	R	R				R
7 Connecticut	R	R	R								V
8 Delaware	V	V	V	V	V	V					V
9 District of Columbia	R	R	R	R	R						R
10 Florida	R	R	R								R
11 Georgia	R	R	R	R	R			R	R		V
12 Hawaii	R		R								
13 Idaho	R	R	R	R	R	R			R		
14 Illinois	R	R	R			R		R			R
15 Indiana	R	R	R	R	R						R
16 Iowa	R	R	R	R				R			R
17 Kansas	R	R	R								R
18 Kentucky	R	R	R								V
19 Louisiana	R		R								R
20 Maine	R	R	R	R	R						V
21 Maryland a	V	V	V	V	V	V			V		V
22 Massachusetts	R	R	R	R	R			R		R	R
23 Michigan	R	R	R	R		R					R
24 Minnesota	R	R	R								V
25 Mississippi	R	R	R								R
26 Missouri	R	R	R								V
27 Montana	R	R	R								
28 Nebraska	R	V	R			R					
29 Nevada	R	R	R	R	R	R			R		R
30 New Hampshire	R	R	R	R	R					R	V
31 New Jersey	R	R	R								R
32 New Mexico	R	R	R								V
33 New York	R	R	R	R	R	R					R
34 North Carolina	V	V	V					V			R
35 North Dakota	R		R								
36 Ohio	R	R	R		R						R
37 Oklahoma	R	R	R								R
38 Oregon	R	R	R	R	R	R			R		
39 Pennsylvania	R		R	V							P
40 Rhode Island	R	R	R	R	R						R
41 South Carolina	R		R								R
42 South Dakota	R	R	R								
43 Tennessee	R		R								R
44 Texas	R	R	R					R			R
45 Utah	R	R	R								
46 Vermont	V	V	V	V	V						V
47 Virginia	R	R	R	R	R	R					R
48 Washington	R		R					R			R
49 West Virginia	R	R	R								V
50 Wisconsin	R	R	R	R	R	R	V				R
51 Wyoming	R	R	R	R	R	R	R				R
52 Puerto Rico	R		R								R
53 Virgin Islands	V	V	V	V	V						V

R = Required; V = Voluntary; P = Pilot

a = Maryland law requires that hospitals or birthing centers must offer testing. However, testing may be refused without reason given, thus, for purposes of this report, Maryland is listed as voluntary.

From: The Council of Regional Networks for Genetic Services. National Newborn Screening Report - 1991.

TABLE 3. SCREENING TECHNIQUES

Disorder	Gene Product	Metabolic Product/ Marker	DNA Variability
G6PD Deficiency		NADPH	
Phenylketonuria		Phenylalanine	*ASO
Hypothyroidism		Thyroxine	
Sickle Cell Disease	Hemoglobin		ASO
Tay Sachs Disease	Hexoseaminidase		
Cystic Fibrosis		Trypsinogen	ASO
LDL Receptor Deficiency	Apoprotein B	Cholesterol	ASO; **Restriction fragment size
Fragile X Mental Retardation			***Trinucleotide repeat
Myotonic Dystrophy			Trinucleotide repeat
Huntington Disease			Trinucleotide repeat
Neural Tube Closure Defects		Alpha Feto-protein	
Down Syndrome		Alpha Feto-protein	
Duchenne Muscular Dystrophy		Creatine kinase	Restriction fragment size; ASO
Congenital Adrenal Hyperplasia		17-Alpha-hydroxy progesterone	

* Allele Specific Oligonucleotides (ASO) are short DNA sequences designed as complementary to specific mutants and are used to probe genomic DNA for given mutants.

** Inherited variation in DNA fragments produced by selected endonuclease enzymes.

***Trinucleotide repeats are multiple numbers of three nucleotide sequence sets, which can be variable in set number among individuals, eg, CAG CAG CAG... etc.

BIBLIOGRAPHY

ASHG Ad Hoc Committe on Breast and Ovarian Cancer Screening. Statement of the American Society of Human Genetics on genetic testing for breast and ovarian cancer predisposition. The American Journal of Human Genetics 55: i-iv, 1994.

Baird P. Opportunity and danger: Medical, ethical and social implications of early DNA screening for identification of genetic risk of common adult onset disorders. In, Knoppers B, Laberge C, (eds), Genetic Screening From Newborns to DNA Typing, pp 279-288, 1990.

Benjamin C, Adam S, Wiggins S, et al. Proceed with care: Direct predictive testing for Huntington Disease. The American Journal of Human Genetics 55: 606-617, 1994.

Burton B, Dillard R, Clark E. The psychological impact of false positive elevations of maternal serum alpha-fetoprotein. American Journal of Obstetrics & Gynecology 151: 77-82, 1985.

Chapman M. Invited editorial: Predictive testing for adult-onset genetic disease: Ethical and legal implications of the use of linkage analysis for Huntington disease. The American Journal of Human Genetics 47: 1-3, 1990.

Cotton R, Rodrigues N, Campbell R. Reactivity of cytosine and thymine in single-base-pair mismatches with hydroxylamine and osmium tetroxide and its application to the study of mutations. Proceedings of the National Academy of Sciences, USA 85: 4397-4401, 1988.

Durfy S. For the benefit of all: Commentary. Hastings Center Report 23: 28-29, 1993.

Eggerding F, Iovannisci D, Brinson E, et al. Fluorescence based oligonucleotide ligation assay for analysis of ceptic fibrosis transmembrane conductance regulator gene mutations. Human Mutation 5: 153-165, 1995.

Forrow L, Arnold R, Parker L. Preventive ethics: Expanding the horizons of clinical ethics. Journal of Clinical Ethics, In press.

Gauthier C. Philosophical foundations of respect for autonomy. Kennedy Institute of Ethics Journal 3: 21-37, 1993.

Goldberg YP, Telenius H, Hayden MR. The molecular genetics of Huntington's disease. Current Opinion in Neurology 7: 325-332, 1994.

Headings V. Revisiting respect for autonomy of the person. A case study of genetic choice. In, From Dispute to Dialogue: Communication and Cooperation within the World of Ethics, Book of Proceedings, Fifth Annual National Conference on Ethics in America. Long Beach, California State University, March 9-11, pp 174-179, 1994.

Headings V. Screening the newborn population for congenital and genetic disorders. Pediatric Reviews & Communications, 2: 317-332, 1988.

Higgins M, Bloch M, Kauana S, et al. Ethical and legal dilemmas arising during predictive testing for adult-onset disease: The experience of Huntington disease. The American Journal of Human Genetics 47: 4-12, 1990.

Highsmith W Jr., Carrier screening for cystic fibrosis. Clinical Chemistry 39: 706-707, 1993.

Juengst E. Human genome research and the public interest: Progress notes from an American science policy experiment. The American Journal of Human Genetics 54: 121-128, 1994.

Kawaguchi Y, Okamoto T, Taniwaki M, et al. CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nature Genetics 8: 221-228, 1994.

King M, Rowell S, Love S. Inherited breast and ovarian cancer: What are the risks? What are the choices? Journal of the American Medical Association 269: 1975-1980, 1993.

Kremer B, Goldberg P, Andrew SE, et al. A worldwide study of the Huntington's Disease mutation: The sensitivity and specificity of measuring CAG repeats. The New England Journal of Medicine 330: 1401-1406, 1994.

Lippman A. Prenatal genetic testing and screening: Constructing needs and reinforcing inequities. American Journal of Law & Medicine 17: 15-50, 1991.

Lishanshi A, Ostrander E, Rine J. Mutation detection by mismatch binding protein, Muts, in amplified DNA: Application to the cystic fibrosis gene. Proceedings of the National Academy of Sciences, USA 91: 2674-2678, 1994.

Mandel J-L. Trinucleotide diseases on the rise. Nature Genetics 7: 453-455, 1994.

Macri J. Critical issues in prenatal maternal serum alpha-fetoprotein screening for genetic anomalies. American Journal of Obstetrics & Gynecology 155: 240-246, 1986.

Macri J, Spencer K, Anderson R. Dual analyte immunoassay -- A new approach to neural tube defect and Down Syndrome screening. Annals of Clinical Biochemistry 29: 390-396, 1992.

Markel H. The stigma of disease: Implications of genetic screening. The American Journal of Medicine 93: 209-215, 1992.

Motulsky A. Invited editorial. Predictive genetic diagnosis. American Journal of Human Genetics 55: 603-605, 1994.

National Advisory Council for Human Genome Research. Statement on use of DNA testing for presymptomatic identification of cancer risk. Journal of the American Medical Association 271: 785, 1994.

Nolan K, Swenson S. New tools, new dilemmas: Genetic frontiers. Hastings Center Report 18: 40-46, 1988.

Orita M, Suzuki Y, Sekiya T, et al. Rapid and sensitive detection of point mutations and DNA polymorphisms using the polymerase chain reaction. Genomics 5: 874-879, 1989.

Parker L. Bioethics for human geneticists: Models for reasoning and methods for teaching. The American Journal of Human Genetics 54: 137-147, 1994.

Pignatti P. In, Humphries S, Malcom S (eds), From Genotype to Phenotype. Oxford, Bios Scientific Publishers, pp. 19-48, 1994.

Pignatti P, Bombieri C, Marigo C, et al. Increased incidence of cystic fibrosis gene mutations in adults with disseminated bronchiectasis. Human Molecular Genetics 4: 635-639, 1995.

Prior T, Papp A, Snyder P, et al. Heteroduplex analysis of the dystrophin gene: Application to point mutation and carrier detection. American Journal of Medical Genetics 50: 68-73, 1994.

Powell S, Peterson G, Krush A, et al. Molecular diagnosis of familial adenomatous polyposis. New England Journal of Medicine 329: 1982-1987, 1993.

Ramus S, Pitt D, Cotton R. Genotype/phenotype correlations: Intellectual phenotypes in untreated PKU patients. International Pediatrics 10: 92-94, 1995.

Ravnich-Glavac M, Gllavoc D, Dean M. Sensitivity of single strand conformation polymorphism and heteroduplex method for mutation detection in the cystic fibrosis gene. Human Molecular Genetics 3: 801-807, 1994.

Romeo G, McKusick V. Phenotypic diversity, allelic series and modifier genes. Nature Genetics 7: 451-453, 1994.

Sarker G, Yoon H, Sommer S. Dideoxy finger printing (ddF): A rapid and efficient screen for the presence of mutations. Genomics 13: 441-443, 1992

Sandholzer C, Saka N, Kark J, et al. Apo(a) isoforms predict risk for coronary heart disease; a study of six populations. Arteriosclerosis and Thrombosis 12: 1214-1226, 1992.

Sheffield V, Cox D, Lerman L, et al. Attachment of a 40-base-pair G+C-rich sequence (GC-Clamp) to genomic DNA fragments by the polymerase chain reaction results in improved detection of single-base changes. Proceedings of the National Academy of Sciences, USA 86: 232-236, 1989.

Sherman S, Martin K, Tayebi N, et al. Individualized neonatal screening, utilizing a d-base computer program. In, Bradford H, Hannon W, Therrell B, Proceedings of the 7th National Neonatal Symposium pp 91-95, 1989.

Soto D, Sukumar S. Improved detection of mutations in the p53 gene in human tumors as single-stranded conformation polymorphs and double-stranded heteroduplex DNA. PCR Methods Applications 2: 96-98, 1992.

Telenius H, Almquist E, Kremer B, et al. Somatic mosaicism in sperm is associated with intergenerational (CAG)n changes in Huntington disease. Human Molecular Genetics 4: 189-195, 1995.

The Cystic Fibrosis Genotype - Phenotype Consortium. Correlation between genotype and phenotype in patients with cystic fibrosis. The New England Journal of Medicine 329: 1308-1313, 1993.

Treacy E, Childs B, Scriver C. Response to treatment in hereditary metabolic disease: 1993 survery and 10-year comparison. The American Journal of Human Genetics 56: 359-367, 1995.

Tsongalis G, Kaufmann W, Wilson S, et al. Rapid screening for p53 mutations with a sensitive heteroduplex detection technique. Clinical Chemistry 40: 485-486, 1994.

Tsui L-C. The spectrum of cystic fibrosis mutations. Trends in Genetics 8: 392-398, 1992.

Wertz D, Fletcher J. Ethics and genetics: An international survey. Hastings Center Report 19 (Suppl): 20-24, 1989.

Wilcken D, Wang X, Greenwood J, et al. Lipoprotein (a) and apolipoproteins B and A-1 in children and coronary vascular events in their grandparents. Journal of Pediatrics 123: 519-526, 1993.