GENETIC TESTING AND COUNSELING: THE FEASIBILITY OF A NATIONWIDE INTERVENTION PROGRAM FOR THE PREVENTION OF MONOGENIC DISEASES

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ABSTRACT

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After the implementation of controls over epidemic and environmental disorders and eliminating malnutrition and endemic diseases, genetic disorders and birth defects are now emerging as a major health problem in technologically developed countries (Khalifa, 1999). Genetic disorders and congenital abnormalities occur in about 2%-5% of all live births, account for up to 30% of pediatric hospital admissions and cause about 50% of childhood deaths in

industrialized countries (Emery, 1995). The purpose of this paper is to present systematic, critical review of literature and data sources pertaining to monogenic diseases, to demonstrate the feasibility of the integration of genetic counseling and testing into primary prevention programs in the United States and to evaluate factors of cost savings based on Health Canada cost-benefit data and monogenic disease incidence data in the United States. The prevalence, costs, and prevention aspects of genetic counseling and testing make this a timely topic to discuss as a major public health issue and warrant the advocacy of the initiation of a nationwide preconception prevention program for the reduction of monogenic diseases in the United States.

CHAPTER I

INTRODUCTION

Until recently, the prevailing diagnostic concept of medical science has been a reactive archetype of the human body as a machine and physicians as the repairmen. The doctor is called upon to repair the faulty mechanisms when they break, similar to the role of an engineer who uses technology to repair a malfunctioning machine (Scriver, 1995). This engineering philosophy has driven medical science for centuries and has influenced medical teaching and shaped the principles of health care. This model is now dependent on advanced and expensive technology, but the escalating costs associated with providing such treatment is making this concept prohibitively expensive (Powles, 1973). It is estimated that the lifelong cost of treating a child with moderate mental retardation (MR) runs to millions of US dollars and it is considerably more for those with severe MR. Medical science has now embarked on a new era — an era of preventive medicine, which entails identifying people at risk of developing diseases and trying to prevent the occurrence of these diseases or alter the course of the diseases before they occur (McKeown, 1976). The role of the physician is slowly evolving from a traditional caregiver/diagnostician to an intermediary between the patient, the patient's genome, and an array of custom

treatment options. Genetics is quickly emerging as the central basic science of biomedical research and is poised to take center stage in clinical medicine as the 21st Century progresses (Khalifa, 1999). It is now more feasible and cost-effective to shift the diagnosis dynamic from treatment to prevention by initiating nationwide intervention programs for the control of monogenic diseases in the United States.

Several programs aimed at preventing or ameliorating genetic disorders have already been implemented in other technologically developed countries where universal health care is the standard. Identifying people at risk of genetic disease has already helped decrease the burden of monogenic diseases, defined as inherited diseases controlled by a single pair of genes, on families and society in countries such as Canada, the United Kingdom and the Netherlands. Early recognition also leads to greater success of treatment and improves outcome and prognosis (Khalifa, 1999). Applying similar programs of early detection such as maternal screening, carrier testing and susceptibility testing can also significantly reduce the impact of these disorders in populations in the United States.

TABLE 1

Total Population, Fertility Rates, and Child Mortality Rates by country for the year 2002

	US	UK	Canada
	Value	Value	Value
Total population [a]	291,038	59,068	31,271
Fertility Rate [b]	2.1	1.6	1.5
Total child mortality rate [c]	8	6.5	5.5

[a] Per 1,000
[b] Number of children per woman per lifetime
[c] Probability of dying under age 5 per 1,000 births

Table 1 presents total population, fertility rates, and child mortality rates by country for the year 2002. This table demonstrates that the UK and Canada have lower total populations and fertility rates than the United States, but the total childhood mortality rates are 20% to 30% higher in the United States than in these other two technologically advanced countries where genetic testing and counseling are commonplace. Could early detection of monogenic diseases though genetic testing and counseling decrease the total childhood mortality rate in the United States?

Monogenic diseases are responsible for a heavy loss of life. The global prevalence of all single gene diseases, also referred to as monogenic diseases, at birth is approximately 1/1000. In Canada, it has been estimated that taken together, monogenic diseases may account for up to 40% of the work of hospital based pediatric practice (WHO, 2004). In a major screening study conducted by Baird et al. in Canada, where 1 million consecutive live births were screened and a population-based register was evaluated, it was found that 53 or more per 1000 live-born individuals could be expected to develop genetic disorders under 25 years of age, while the estimate would be 79 per 1000 live-born individuals if all congenital anomalies were considered as part of the genetic load (Baird, 1998). Of the genetic disorders, single-gene disorders occurred in 3.6 per 1000 (autosomal recessive = 1.7 per 1000; autosomal dominant = 1.4 per 1000 and X-linked recessive = 0.5 per 1000 {*see Definition of Terms p. 13*}) (El-Hazmi, 1999).

Genetics and monogenic diseases

The Human Genome Project (HGP) has been instrumental in creating the field of genomics. What is genomics? This is defined as the study of how genes are used by the body; the primary objective is to understand genetic material on a large scale and determine how the process can be manipulated to treat illness and revolutionize health care delivery. The main difference between genomics and genetics is that genetics scrutinizes the functioning and composition of the single gene whereas genomics addresses all genes and their interrelationships in order to identify their combined influence on the growth and development of the organism.

Today's medical industry is building upon the knowledge, resources, and technologies emanating from the HGP to further understanding of genetic contributions to human health. As a result of this expansion of genomics into human health applications, the field of genomic medicine was born. Genetics is playing an increasingly important role in the diagnosis, monitoring, and treatment of diseases (Bezold, 2002).

All diseases have a genetic component, whether inherited or resulting from the body's response to environmental stresses like viruses or toxins. The successes of the HGP have enabled researchers to better diagnose and predict disease and disease susceptibility by pinpointing errors in genes, the smallest units of heredity that cause or contribute to disease.

An increasing number of gene tests are becoming available commercially, although the scientific community continues to debate the best way to deliver

them to the public and medical communities that are often unaware of their scientific and social implications. While some of these tests have greatly improved and even saved lives, scientists remain unsure of how to interpret many of them. Also, patients taking the tests face significant risks of jeopardizing their employment or insurance status. And because genetic information is shared, these risks can extend beyond them to their family members as well (Maxwell, 2001).

The nature and frequency of genetic disorders differ in different populations. Several extensive population studies have been conducted and have provided an insight into the frequency of these disorders in some populations. Over 6000 such disorders have been identified (Buyrse, 1999) and many more are expected to be unveiled since it is recognized that the total human genetic component carries between 50,000 and 100,000 structural genes. These disorders may be dominant, recessive, or sex-linked (i.e. Y- or X-linked). They follow a very clear pedigree pattern of inheritance and examples of a few of these disorders with the approximate frequency will be presented in tables on page 7 (McKusick, 1994).

Geneticists group genetic disorders into three categories. The focus of this thesis is on single gene disorders or monogenic diseases. These diseases result from modifications in a single gene occurring in all cells of the body. Though relatively rare, they affect millions of people worldwide. Scientists currently estimate that over 6,000 of human diseases are known to be monogenic. Pure genetic diseases are caused by a single error in a single gene

in the human DNA. The nature of disease depends on the functions performed by the modified gene. The single-gene or monogenic diseases ordinarily exhibit one of three patterns of inheritance and can be classified into the three main categories displayed on page 7- autosomal dominant disorders displayed in Table 2, autosomal recessive disorders displayed in Table 3, and X-linked disorders displayed in Table 4 (WHO, 2004).

If a particular disease shows one of the three Mendelian patterns of inheritance, its pathogenesis, no matter how complex, must be due to an abnormality at a single site in the genome, usually involving a single protein. The mutant gene and protein for many common Mendelian disorders are known even when the full pathogenesis of a disorder is not known (Scriver, 2000). All human beings have two sets or copies of each gene called "allele"; one copy on each side of the chromosome pair. Recessive diseases are monogenic disorders that occur due to damages in both copies or allele. Dominant diseases are monogenic disorders that involve damage to only one gene copy. X linked diseases are monogenic disorders that are linked to defective genes on the X chromosome which is the sex chromosome. These alleles, or copies of each gene, are expressed equally in men and women, more so in men as they carry only one copy of X chromosome (XY) whereas women carry two (XX). The following tables document incidence rates of the most common single gene disorders in the United States, Canada, and the United Kingdom. The disorders include the International Classification of Diseases- Ninth Edition (ICD-9 code) and are categorized by genetic category for diagnosis purposes.

For Canadian incidence rates, statistics were retrieved from the National Canadian Health Surveillance Registry (HSR), Canadian Institution for Health Information (CIHI) and the Canadian Congenital Abnormalities Surveillance Network (CCASN) with the cooperation of Health Canada. Incidence rates from the United Kingdom (UK) were retrieved from the National Congenital Abnormality System (NCAS) with the cooperation of UK's National Health Service (NHS) and the United Kingdom's Genetic Interest Group (GIG).

Retrieving US incidence rates was much more challenging. The United States is one of the only technologically advanced countries that do not maintain a national surveillance system for congenital abnormalities. Only California and Metropolitan Atlanta maintain such surveillance systems in the US. Incidence rates had to be piece-milled from non-profit organizations, government agencies, and disease-specific informational websites.

TABLE 2

Frequencies of the Most Common Autosomal Dominant Disorders

ICD-9, Dominant Disorder		US Rate[a]	UK Rate[a]	Canada Rate[a]
211.0	Familial Polyposis	0.01	0.10	0.01
237.70	Neurofibromatosis	0.20	0.40	0.84
256.4	Multiple exostoses	0.01	0.50	0.001
282.0	Congenital/ Heredity spherocytosis	0.08	0.20	0.42
333.4	Huntington's Disease	0.01	0.50	0.01
359.2	Myotonic Dystrophy	0.07	0.20	0.23
387.9	Otosclerosis	0.80	1.00	0.18
759.89	Polycystic kidney disease	2.00	0.80	0.35

[a] Per 1,000 live births

TABLE 3

Frequencies of the Most Common Autosomal Recessive Disorders

ICD-9, Recessive Disorder		US Rate[a]	UK Rate[a]	Canada Rate[a]
277.0	Cystic fibrosis	0.01	0.40	0.23
770.2	Alpha-1-antitrypsin deficiency/Emphysema	0.10	0.20	0.20
270.1	Phenylketonuria	0.20	0.10	0.64
255.2	Congenital adrenal hyperplasia	0.30	0.10	0.10
335.0	Spinal muscular atrophy	0.10	0.10	0.34
282.60	Sickle cell anemia	2.00	0.10	0.32
330.10	Tay Sachs	0.10	*	0.10
282.4	Thalassamia	0.005	0.05	0.02

[a] Per 1,000 live births
* Not Available

TABLE 4

Frequencies of the Most Common X-Linked Disorders

ICD-9, X-Linked Disorder		US Rate[a]	UK Rate[a]	Canada Rate[a]
759.83	Fragile X syndrome	0.30	0.50	0.20
359.1	Duchenne muscular dystrophy	0.60	0.30	0.10
756.59	Conradi-Hunermann syndrome	0.01	0.20	0.10
286.0	Hemophillia	0.04	0.10	0.08
368.59	Red-green color blindness	2.00	1.00	0.08

[a] Per 1,000 live births

Genetic screening, testing, and counseling

Genetic screening is the monitoring of a population to identify affected fetuses, or to determine those members of the population who, despite being apparently normal, have genotypes, defined as the genetic identity of an individual that does not show as outward characteristics, that are associated with diseases, or may lead to diseases in their offspring (Principles of screening, 1997). Genetic screening thus serves several objectives. First, it can lead to therapy, as in the case of newborn screening, which aims for the earliest possible recognition of disorders so that intervention can prevent the serious consequences of these diseases. Secondly, screening can identify those whose

pregnancies are at increased risk of producing offspring with serious genetic abnormalities. They can then be counseled on their reproductive options, including prenatal diagnosis and treatment (Khalifa, 1999).

Genetic testing identifies abnormalities in a person's genes, or the presence/absence of key proteins whose production is directed by specific genes. Abnormalities in either could indicate an inherited disposition to a disorder. Genetic testing includes both gene testing (DNA testing) and biochemical testing (protein testing). Genetic testing can be predictive, discovering whether an individual has an inherited disposition to a certain disease, before symptoms appear. Genetic tests can also confirm a diagnosis if symptoms are present. Tests can determine whether a person is a carrier for the disease (NHGRI, 2004).

Ideally, genetic screening and testing should be supported by genetic counseling, and is most often used to modify the assessment of risk of Mendelian inherited disease in high-risk individuals for the purpose of personal decision making. Genetic counseling was also developed to address the medical and social consequences of single gene disorders and has become an integral part of genetic testing (Pagon, 2002). Genetics counselors are health care professionals with specialized graduate degrees and experience in medical genetics and counseling. Genetic counselors work as members of health care teams providing information and support to individuals or families who have genetic disorders or may be at risk for inherited conditions (NHGRI, 2004). Genetic counseling as currently practiced is focused on the assessment of

genetic risk, education of at risk family members about disease manifestations and management, education regarding reproductive options, and provision of psychological and emotional support to develop coping strategies for largely untreatable diseases (Pagon, 2002).

In some technologically developed countries, several programs are currently in place to identify individuals at risk of genetic disorders amenable to prevention or treatment. As technology evolves, newer program and services are being introduced, once their merit becomes evident. Law mandates some of these programs, but other programs are voluntary. In Canada, where health services are constitutionally guaranteed to each individual, the preventive genetic programs are universally available to everyone. The most significant measure is genetic screening and Canada has been a leader in taking the initiative to apply the principles of genetic screening in the health care system (Khalifa, 1999). The currently available services in Canada to identify at-risk individuals for genetic disorders through genetic screening include maternal serum screening, carrier screening, presymptomatic testing, susceptibility testing, and preimplantation testing.

Screening should not be expected to detect all patients. It is unrealistic to expect any screening program to identify all affected individuals (Principles of screening, 1997). Unless mandated by law, screening for genetic diseases should be voluntary and with the patient's informed consent. Newborn screening for metabolic diseases is, however, legally required in most provinces and states (Khalifa, 1999). If screening is mandated by law, then the ability to alter the

outcome should be a primary consideration.

Reliable methods of assessment should also be a prerequisite. The assay to be used for genetic screening should have a high predictive value. Because genetic disorders are individually rare, even low false-negative rates could result in a given abnormal value being more likely to be a false-positive than a true-positive value (Principles of screening, 1997).

Mechanisms should be in place to handle and deal with these inevitable unexpected problems that will arise in any screening program. In most of the neonatal screening programs in North America, advisory committees have been established to monitor the programs and deal with such problems. In addition, no genetic screening program will be successful if not accompanied by extensive educational activities aimed at both the general public and health care providers (Principles of screening, 1997). Without proper education, information and even counseling, the general public and health care providers may not effectively participate in these programs. It is very important for health professionals working among specific populations, who have been able to identify the impact of genetic diseases on them, to start to implement some of these preventative measures. The resources and expertise are available and populations deserve such services (Khalifa, 1999).

Cost benefits

How do we determine what universally satisfies the criteria for cost benefits for genetic screening and counseling (Khalifa, 1999). How do we measure the cost of newborn screening to justify the financial and emotional

savings of preventing or detecting affected individuals?

Genetic diseases are chronic in nature with no cure and they often require lifelong medical attention, expensive supportive and symptomatic therapy and specialist care (Czeizal, 1984). The impact of a given disease may vary with the severity of the disease itself and also varies with individuals and families. In general, these conditions are a leading cause of spontaneous abortion, neonatal death, increased morbidity in children and adults and an increase in childhood mortality. They are a significant health care and psychosocial burden for the patient, the family, the health care system and the community as a whole (WHO, 2004).

Population screening is usually performed only if the abnormal finding can prevent an affected birth or change the clinical management, and consequently result in a favorable outcome and overall cost savings. Neonates are screened for those metabolic diseases that can be treated, such as PKU and hypothyroidism, but not for those disorders that are untreatable, such as mucopolysaccharidosis or Tay-Sachs disease (Khalifa, 1999). Hence, the best approach is to prevent the occurrence of genetic diseases, which have serious consequences, by identifying the abnormality prenatally (El-Hazmi, 1999).

This paper will review a select group of monogenic genetic disorders, their impact on health care delivery systems and the general framework required to prevent and control these disorders.

TABLE 5

Current Funding Sources for Newborn screening programs in US

Funding Source	Percentage of program expenditures
Fees	64
Maternal and Child Health Services Block Grant	5
Medicaid [a]	10
Other state funds	19
Other funds [b]	2

[a] Includes federal and state contributions
[b] Includes the Preventative Health and Health Services Block Grant

Definition of terms

Allele - One of the variant forms of a gene at a particular locus, or location, on a chromosome. Different alleles produce variation in inherited characteristics such as hair color or blood type.

Alpha-1-antitrypsin deficiency (A1AD) – aka. Familial / heredity emphysema; A1AD is a hereditary disorder characterized by low levels of a protein called alpha-1-antitrypsin (A1AT) which is found in the blood. This deficiency may predispose an individual to several illnesses but most commonly appears as emphysema, less commonly as liver disease, or more rarely, as a skin condition called panniculitis. A deficiency of A1AT allows substances that break down protein (proteolytic enzymes) to attack various tissues of the body. This results in destructive changes in the lungs (emphysema) and may also affect the liver and joints.

Amino acids - A group of 20 different kinds of small molecules that link together in long chains to form proteins. Often referred to as the "building blocks" of proteins.

Autosomal dominant - pattern of Mendelian inheritance whereby an affected individual possesses one copy of a mutant allele and one normal allele. Individuals with autosomal dominant diseases have a 50-50 chance of passing the mutant allele and hence the disorder onto their children.

Birth defect - A structural, functional, or metabolic abnormality present at birth that results in physical or mental disability or is fatal.

BRCA1 / BRCA2 - The first breast cancer genes to be identified. Mutated forms of these genes are believed to be responsible for about half the cases of inherited breast cancer, especially those that occur in younger women.

Carrier - An individual who possesses one copy of a mutant allele that causes disease only when two copies are present. Although carriers not affected by the disease, two carriers can produce a child who has the disease.

Cell - The basic unit of any living organism. It is a small, watery, compartment filled with chemicals and a complete copy of the organism's genome.

Chromosome - One of the threadlike "packages" of genes and other DNA in the nucleus of a cell. Different kinds of organisms have different numbers of chromosomes. Humans have 23 pairs of chromosomes, 46 in all: 44 autosomes and two sex chromosomes. Each parent contributes one chromosome to each pair, so children get half of their chromosomes from their mothers and half from their fathers.

Cloning - The process of making copies of a specific piece of DNA, usually a gene. When geneticists speak of cloning, they do not mean the process of making genetically identical copies of an entire organism.

Congenital - Any trait or condition that exists from birth.

Congenital adrenal hyperplasia (CAH) – this autosomal recessive disorder refers to a group of disorders that result from the impaired ability of the adrenal glands to produce vital steroid hormones (corticosteroids), two of which, glucocorticoids and mineralocorticoids, are normally active in the body.

Congenital spherocytosis – a rare blood disorder characterized by defects within red blood cells (intracorpuscular) that result in a shortened survival time for these cells. Red blood cells (erythrocytes) normally circulate for a few months and when they die off are replaced by new erythrocytes.

Conradi-Hunermann syndrome - a form of chondrodysplasia punctata, a group of rare, genetic disorders of skeletal development (skeletal dysplasias) characterized by unusual, "dotlike" (punctate) opacities representing abnormal accumulations of calcium salts (calcifications) within the growing ends of long bones (i.e., "stippled" epiphyses) and other regions. Conradi-Hunermann syndrome is commonly associated with mild to moderate growth deficiency; disproportionate shortening of long bones, particularly those of the upper arms (humeri) and the thigh bones (femora); short stature; and/or curvature of the spine.

Cystic fibrosis - A hereditary disease whose symptoms usually appear shortly after birth. They include faulty digestion, breathing difficulties and respiratory infections due to mucus accumulation, and excessive loss of salt in sweat. In the past, cystic fibrosis was almost always fatal in childhood, but treatment is now so improved that patients commonly live to their 20s.

Deoxyribonucleic acid (DNA) - The chemical inside the nucleus of a cell that carries the genetic instructions for making living organisms.

DNA replication - The process by which the DNA double helix unwinds and makes an exact copy of itself.

DNA sequencing - Determining the exact order of the base pairs in a segment of DNA.

Dominant - A gene that almost always results in a specific physical characteristic, for example, a disease, even though the patient's genome possesses only one copy. With a dominant gene, the chance of passing on the gene (and therefore the disease) to children is 50-50 in each pregnancy.

Double helix - The structural arrangement of DNA, which looks something like an immensely long ladder twisted into a helix, or coil. The sides of the "ladder" are formed by a backbone of sugar and phosphate molecules, and the "rungs" consist of nucleotide bases joined weakly in the middle by hydrogen bonds.

Duchenne muscular dystrophy – aka. Pseudohypertrophic; One of nine types of muscular dystrophy, a group of genetic, degenerative diseases primarily affecting voluntary muscles. An absence of dystrophin, a protein that helps keep muscle cells intact.

Duplication - A particular kind of mutation: production of one or more copies of any piece of DNA, including a gene or even an entire chromosome.

Enzyme - A protein that encourages a biochemical reaction, usually speeding it up. Organisms could not function if they had no enzymes.

Familial polyposis - group of rare inherited disorders of the gastrointestinal system. Initially it is characterized by benign growths (adenomatous polyps) in the mucous lining of the gastrointestinal tract.

Fragile X syndrome – the second most frequent genetic cause of mental retardation. The disorder is one of a group of diseases that results from an unusual kind of mutation: an expansion of a repeating sequence of three letters of the DNA code, called a triplet repeat or trinucleotide repeat.

Gene - The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein.

Gene pool - The sum total of genes, with all their variations, possessed by a particular species at a particular time.

Gene therapy - An evolving technique used to treat inheritied diseases. The medical procedure involves either replacing, manipulating, or supplementing nonfunctional genes with healthy genes.

Genetic code (ATCG) - The instructions in a gene that tell the cell how to make a specific protein. A, T, G, and C are the "letters" of the DNA code; they stand for the chemicals adenine, thymine, guanine, and cytosine, respectively, that make up the nucleotide bases of DNA. Each gene's code combines the four chemicals in various ways to spell out 3-letter "words" that specify which amino acid is needed at every step in making a protein.

Genetic counseling - A short-term educational counseling process for individuals and families who have a genetic disease or who are at risk for such a disease. Genetic counseling provides patients with information about their condition

and helps them make informed decisions.

Genetic mapping - (Also known as a linkage map) a chromosome map of a species that shows the position of its known genes and/or markers relative to each other, rather than as specific physical points on each chromosome.

Genetic marker - A segment of DNA with an identifiable physical location on a chromosome and whose inheritance can be followed. A marker can be a gene, or it can be some section of DNA with no known function.

Genetic screening - Testing a population group to identify a subset of individuals at high risk for having or transmitting a specific genetic disorder.

Genome - All the DNA contained in an organism or a cell, which includes both the chromosomes within the nucleus and the DNA in mitochondria.

Genotype- The genetic identity of an individual that does not show as outward characteristics.

Hemophilia - A sex-linked inherited bleeding disorder that generally only affects males. The disorder is characterized by a tendency to bleed spontaneously or at the slightest injury because of the lack of certain clotting factors in the blood.

Human Genome Project - An international research project to map each human gene and to completely sequence human DNA.

Huntington's disease - A degenerative brain disorder that usually appears in mid-life. Its symptoms, which include involuntary movement of the face and limbs, mood swings, and forgetfulness, get worse as the disease progresses. It is generally fatal within 20 years.

Inherited - Transmitted through genes from parents to offspring.

Intellectual property rights - Patents, copyrights, and trademarks.

Linkage - The association of genes and/or markers that lie near each other on a chromosome. Linked genes and markers tend to be inherited together.

Mapping – The process of deducing schematic representations of DNA. Three types of DNA maps can be constructed: physical maps, genetic maps, and cytogenetic maps, with the key distinguishing feature among these three types being the landmarks on which they are based.

Marker – Also known as a genetic marker, a segment of DNA with an identifiable physical location on a chromosome whose inheritance can be followed. A

marker can be a gene, or it can be some section of DNA with no known function.

Mendel, Johann (Gregor) – Austrian biologist, born in 1822 and died in 1884, who laid the foundations for the science of genetics. Mendel was a monk whose controlled experiments with breeding peas in the monastery garden led him to conclude that the heritable units we now call genes were not blends of parental traits but separate physical entities passed individually in specific proportions from one generation to the next. Mendel's discoveries were ignored for several decades, but other biologists finally recognized their significance early in the 20th century.

Mendelian inheritance – Manner in which genes and traits are passed from parents to children. Examples of Mendelian inheritance include autosomal dominant, autosomal recessive, and sex-linked genes.

Metabolic - chemical changes that take place within living cells

Monogenic diseases - inherited diseases controlled by a single pair of genes, a.k.a. single gene disorders.

Multiple exostoses - a rare skeletal disorder that is inherited in an autosomal dominant fashion. As the name suggests, this disorder is characterized by multiple bony growths or tumors (exostoses), often on the growing end (epiphysis) of the long bones of the legs, arms, and digits. These bony growths are covered by cartilage and usually continue to grow until shortly after puberty. They may cause deformities, especially of the ankle, knee, and wrist.

Mutation - A permanent structural alteration in DNA. In most cases, DNA changes either have no effect or cause harm, but occasionally a mutation can improve an organism's chance of surviving and passing the beneficial change on to its descendants.

Myotonic dystrophy - an inherited disorder involving the muscles, vision, and endocrine glands. It may also cause mental deficiency and loss of hair. The more obvious features of the disorder are muscle rigidity and the inability to relax a muscle or set of muscles after contraction. Onset of this rare disorder usually occurs during early adulthood. However, it may occur at any age and is extremely variable in degree of severity.

Neurofibromatosis - An inherited progressive disorder in which tumors form on peripheral nerves. The tumors can be severely disfiguring and can also result in loss of hearing and vision, cancer, epilepsy, bone deformities, and learning disabilities.

Otosclerosis - the abnormal growth of bone of the middle ear. This bone prevents structures within the ear from working properly and causes hearing loss. For some people with otosclerosis, the hearing loss may become severe.

Patent - When applied to genetics, the government regulations or requirements conferring the right or title to an individual or organization to genes if there has been substantial human intervention.

Pedigree - A simplified diagram of a family's genealogy that shows family members' relationships to each other and how a particular trait or disease has been inherited.

Phenotype – The observable traits or characteristics of an organism, for example hair color, weight, or the presence or absence of a disease.

Phenylketonuria (PKU) – an inborn error of metabolism that is detectable during the first days of life with appropriate blood testing (e.g., during routine neonatal screening). PKU is characterized by absence or deficiency of an enzyme (phenylalanine hydroxylase) that is responsible for processing the essential amino acid phenylalanine.

Physical map - A chromosome map of a species that shows the specific physical locations of its genes and/or markers on each chromosome. Physical maps are particularly important when searching for disease genes by positional cloning strategies and for DNA sequencing.

Polycystic kidney disease – Polycystic Kidney Diseases are inherited renal disorders characterized by the presence of multiple cysts in both kidneys (bilateral renal cysts). Normal kidney tissue is replaced by fluid-filled sacs or cysts of varying sizes that become larger as the disease progresses.

Protein – A large complex molecule made up of one or more chains of amino acids. Proteins perform a wide variety of activities in the cell.

Recessive - A genetic disorder that appears only in patients who have received two copies of a mutant gene, one from each parent.

Recombinant DNA - A variety of techniques that molecular biologists use to manipulate DNA molecules to study the expression of a gene.

Red-green color blindness – an Inherited color vision problems affect both eyes equally, are usually present at birth, and do not change during a person's life. The most common color vision problems are inherited problems that make it harder to see red or green, so that it becomes difficult to distinguish between shades of these two colors.

Ribonucleic acid (RNA) - A chemical similar to a single strand of DNA. In RNA, the letter U, which stands for uracil, is substituted for T in the genetic code. RNA delivers DNA's genetic message to the cytoplasm of a cell where proteins are made.

Sex chromosome - One of the two chromosomes that specify an organism's genetic sex. Humans have two kinds of sex chromosomes, one called X and the other Y. Normal females possess two X chromosomes and normal males one X and one Y.

Sex-linked - Located on the X chromosome. Sex-linked (or x-linked) diseases are generally seen only in males.

Sickle cell disease - A blood condition seen most commonly in people of African ancestry. The disorder is caused by a single base pair change in one of the genes that codes for hemoglobin, the blood protein that carries oxygen. This mutation causes the red blood cells to take on a sickle shape, rather than their characteristic donut shape. Individuals who suffer from sickle cell disease are chronically anemic and experience significant damage to their heart, lungs, and kidneys.

Spinal muscular atrophy (SMA) - caused by a deletion of the SMN gene on chromosome 5 is an inherited progressive neuromuscular disorder characterized by degeneration of groups of nerve cells (motor nuclei) within the lowest region of the brain (lower brainstem) and certain motor neurons in the spinal cord (anterior horn cells). Motor neurons are nerve cells that transmit nerve impulses from the spinal cord or brain (central nervous system) to muscle or glandular tissue.

Syndrome - The group or recognizable pattern of symptoms or abnormalities that indicate a particular trait or disease.

Tay-Sachs - a rare, neurodegenerative disorder in which deficiency of an enzyme (hexosaminidase A) results in excessive accumulation of certain fats (lipids) known as gangliosides in the brain and nerve cells. This abnormal accumulation of gangliosides leads to progressive dysfunction of the central nervous system.

Thalassamia - a rare blood disorder characterized by a marked increase in F hemoglobin and a decrease in the production of certain oxygen carrying proteins in red blood cells (beta polypeptide chains in the hemoglobin molecule).

Sources of data

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Methodology

This paper will present an overview of monogenic diseases, including mechanisms of inheritance and approximate frequencies of the most common disorders such as cystic fibrosis, sickle cell anemia, hemophilia, etc. It will also demonstrate the feasibility of the integration of genetic counseling and testing into primary prevention programs in the United States verses the prevailing policy of secondary prevention through newborn screening. This paper will present the public health implications of such a program and the strategies necessary to implement the program and prerequisites necessary to determine cost-effectiveness of such a program. This paper will also include an extensive discussion of the ethical, legal and social impediments that will need to be overcome in the United States in order to implement a nationwide preconception prevention program for the reduction of monogenic diseases.

This paper will also present an overview of Baird et al.'s 1998 population study of genetic disorders in children and young adults in Canada and the Health Canada cost-benefit data. Based on lack of monogenic disorder cost data available in the in the United States, this paper will use the same methodology and assume the same treatment costs utilized by Health Canada and apply it to monogenic disorder incidence data in the United States to demonstrate the feasibility of the integration of nationwide preconception prevention program for the reduction of monogenic diseases in United States and to evaluate factors of cost savings.

Significance of problem

After implementing controls over epidemic and environmental disorders and eliminating malnutrition and endemic diseases, genetic disorders and birth defects are now emerging as a major health problem in technologically developed countries (Khalifa, 1999). There are more than 6000 single-gene Mendelian disorders described to date. Of total deliveries, 16% involve birth defects, and almost 50% of these are major (i.e. they have medical, surgical or cosmetic consequences). About 50% of all pediatric admissions to major hospitals involve birth defects or genetic diseases. After accidents, genetic disorders are the leading cause of death in children in North America (Buyrse, 1999). In the United States, 250,000 births annually involve major birth defects, and over 10 million American men and women currently have birth defects. In Canada, it is estimated that 60% of Canadians will experience a disease with a significant genetic component in their lifetime (Baird, 1998). Globally, prevalence of all single chromosome diseases is 1/1000 (World Health Organiztion, 2004).

Now that the technology exits and the expenditures are no longer cost prohibitive, it is time to shift the diagnosis dynamic from treatment to prevention. The feasibility of the integration of nationwide preconception prevention program for the reduction of monogenic diseases in United States can be demonstrated by applying U.S. monogenic disorder incidence data to the Health Canada cost-effectiveness analysis model to demonstrate the cost benefits.

CHAPTER II

IMPORTANCE OF GENETIC TESTING AND COUNSELING

Depending on the province (Canada) or state (the United States), virtually all neonates are screened for between 2 and 13 genetic and non-genetic conditions. The combined number of infants screened in the neonatal period, and the number of neonatal screening tests performed, far exceed those for any other type of genetic test (Hiller, 1997).

In the United States, newborn screening is one of the largest disease prevention programs, reaching approximately 4 million newborns each year. This program is managed by the Newborn Screening Branch, Division of Laboratory Sciences (a division of Centers for Disease Control [CDC] in Atlanta), which operates the Newborn Screening Quality Assurance Program (NSQAP). NSQAP is a voluntary, non-regulatory program to help state health departments and their laboratories maintain and enhance the quality of test results. The program is operated in partnership with the Association of Public Health Laboratories (CDC, 2004).

All states screen newborns for certain metabolic birth defects. These conditions cannot be seen in the newborn, but can cause physical problems, mental retardation and, in some cases, death. When test results show that the

baby has a birth defect, early diagnosis and treatment can make the difference between lifelong disabilities and healthy development. Each year approximately 3,000 babies with severe disorders are identified in the United States using these newborn screening programs (Newborn screening, 2003). The March of Dimes recommends that all newborns be screened for at least nine metabolic disorders and hearing loss. Of the nine disorders, the following three are single gene disorders: phenylketonuria (PKU), congenital adrenal hyperplasia (CAH) and sickle cell disease (March of Dimes' state report card, 2004).

Unfortunately, newborn screening currently available is not being fully utilized. The March of Dimes estimates seventy percent of babies in the U.S. are born in states that still fail to carry out the nine core newborn screening tests (March of Dimes report card, 2004). Few parents realize that the extent of newborn testing depends entirely on the state in which their baby is born. The number of screened disorders continues to vary greatly by state and some screening programs sit idle due to lack of funding (March of Dimes report, 2004). Parents seeking screening for disorders not currently performed by their state must arrange privately for their newborn to be screened, often with additional out-of-pocket expense.

Currently, the following 21 states screen for the March of Dimes-recommended list of metabolic disorders: Alaska, Connecticut, Hawaii, Idaho, Illinois, Indiana, Iowa, Maine, Maryland, Massachusetts, Mississippi, Nevada, New York, North Dakota, Oregon, Rhode Island, Tennessee, Vermont, Virginia, Washington, and Wisconsin. These states account for about 1.3 million of the

approximately 4 million live births each year in the U.S. This translates to only about 32 percent of babies are born in states that carry out the recommended screening. Seven states-- Louisiana, Missouri, Montana, Nebraska, New Hampshire, Pennsylvania, South Dakota -- are testing only selected populations within the state or are running pilot programs that do not include all babies (March of Dimes report card, 2004).

The field of newborn screening is rapidly expanding because of new technologies and genetic discoveries and is no longer cost-prohibitive. All states should make newborn screening a top priority and also integrate a prevention strategy by incorporating genetic screening and counseling into the existing testing programs. Just as parents have the right to know the positive health information of their unborn babies, so too should they be privy to any and all potentially unfavorable information so they can make educated choices about their child's future. Preconception information and services for family planning would help reduce the number of high-risk pregnancies and children born with monogenic disorders. Not every treatable condition is, or should be, screened in newborns, but should be detected prenatally. For how many disorders does the cost of newborn screening justify the financial and emotional savings of detecting the affected individuals prior to conception (Khalifa, 1999).

Cost-effectiveness

Determining how best to use these technologies will require consideration of the clinical benefits and costs, both to individuals and to society (Higashi et al., 2000). Cost-effectiveness analysis (CEA) is one tool decision-makers can use to

assess and potentially improve the performance of their health systems. It indicates which interventions provide the highest "value for money" and helps them choose the interventions and programs that maximize health for the available resources (Who-Choice, 2004). Cost-effectiveness analysis is increasingly being used to weigh these factors and thus to determine the relative value of new technologies.

The fundamental principle of cost-effectiveness analysis is that choices must be made between alternative uses of limited resources. A cost-effectiveness analysis can illustrate the relationship between the net resources used and the net health benefits gained for a specific clinical intervention (such as genetic testing) compared with an alternative (such as phenotypic testing). It can illustrate the tradeoffs with different policy choices and can provide quantitative insight into the relative importance of different parameters, thus helping to determine which variables are most important to measure in clinical research (Goldie, 2001).

The cost-effectiveness of genetic testing will depend on the value of this information to patients and to society. Susceptibility is determined by the risk of disease among gene carriers (i.e., gene penetrance), which may vary substantially between high-risk families and the general population. Therefore, the most critical parameters in cost-effectiveness analyses of genetic testing will be the target population, the prevalence of the mutation, and gene penetrance (Arcos-Burgos, 2002).

For a cost-effectiveness analysis to be useful in informing policy, it should consider all clinical and economic events triggered by the positive test result. A genetic testing strategy is less likely to be cost-effective when penetrance is incomplete, when effective alternative tests exist, and when there is no treatment for the disease (Higashi et al., 2000). Following a description of several specific tools and methods for generalized cost-effectiveness analysis that are particularly relevant to genetic screening and are recommended by the World Health Organization's Who-Choice program.

(1) Develop a standardized method for cost effectiveness analysis that can be applied to all interventions in different settings;

(2) Develop and disseminate tools required to assess intervention costs and impacts at the population level;

(3) Determine the costs and effectiveness of a wide range of health interventions, undertaken by themselves or in combination;

(4) Summarize the results in regional databases that will be available on the World Wide Web;

(5) Assist policy makers and other stakeholders to interpret and use the evidence

The results of a cost-effectiveness analysis can be summarized using an incremental cost-effectiveness ratio, which represents the incremental price of obtaining a unit health effect (usually dollars per QALY) as a result of a given clinical intervention when compared to the next best alternative. The uncertainty in a cost-effectiveness analysis is evaluated by sensitivity analysis, which involves testing the stability of the conclusions over a range of parameter estimates and structural assumptions. In the context of genetic testing, special attention should be paid to understanding the implications of varying parameters

governing the frequency and severity of the clinical and economic consequences of the disease, the phenotypic expression of genetic variation, and the genetic test characteristics (Goldie, 2001).

Cost-effectiveness model

Despite numerous attempts to acquire Health Canada Health Surveillance Registry (HSR) cost-benefit data through formal channels and via creative, unconventional channels, I was not allowed access to the data nor the methodology due to confidentiality reasons. Therefore, the Health Canada methodology and data required to perform the cost effectiveness analysis of US data was not available and I was unable to complete my thesis as proposed. In lieu of the cost effectiveness analysis of US data, this section will present a cost effectiveness model that can be used to perform the cost effectiveness analysis (CEA) for the evaluation of monogenetic diseases.

The cost effectiveness analysis should begin with accurate population data and cost data. In a significant population study, *Genetic Disorders in Children and Young Adults: A Population Study*, conducted by Baird et al., in Canada, the population-based register Health Surveillance Register (HSR) maintained by Health Canada was evaluated for the purposes of genetic risk assessment. This information in this database is provided by a number of government agencies concerned with health, rehabilitation and human resources and by hospitals, treatment and rehabilitation centers, voluntary agencies, physicians, and the vital registration system. The HSR has been widely used for studies of particular hereditary diseases and congenital malformations. The

existence of this ongoing database makes it possible to estimate the number of individuals born within the population who have been identified a having a disorder with a wholly or partially genetic cause. Confidentiality of the personal information contained in the records is maintained under the same legal safeguards that are applied to vital statistics. After screening over 1 million consecutive live births, this study determined that of the genetic disorders, single-gene disorders occurred in 3.6 per 1000 (autosomal recessive = 1.7 per 1000; autosomal dominant = 1.4 per 1000 and X-linked recessive = 0.5 per 1000) (Baird et al, 1989).

In preparation for conducting a cost-effectiveness analysis and using the Baird study as a model, the single gene disorders used in Tables 2-4 in Chapter 1 were selected using the following three criteria:

(1) The disease must have only one ICD-9 diagnostic code for diagnosis

(2) Genetic testing and identification analysis must already exist and be readily available to the consummer

(3) The monogenic disease incidence rate had to be significant enough to measure at rate greater than or equal to 0.001 in 1,000.

The selected single gene disorders were then sorted into the following three inheritance categories: (1) autosomal dominant disorders, (2) autosomal recessive disorders, and (3) X-linked disorders.

In the 1997 van der Reit article *Cost effectiveness of DNA diagnosis for four monogenic diseases*, the costs and benefits associated with DNA diagnosis of subjects at risk of having a child with a monogenic disease and who seek

genetic counseling because of their reproductive plans are predicted under various assumptions using a mathematical model. Four monogenic diseases were considered: cystic fibrosis, Duchenne muscular dystrophy, myotonic dystrophy, and fragile X syndrome. Counseling (triggered by previous information) on the basis of DNA diagnosis was compared to the situation that only risk evaluation based on pedigree analysis is possible. The results show for each disease that with DNA diagnosis, couples can be more confident in choosing (further) offspring leading to the birth of more healthy children while the number of affected children is reduced. The costs minus savings within the health care sector depend on the prior risks and on the future burden of the monogenic illness under consideration. DNA diagnosis of relative "low" prior risks of a child with CF (for example, 1:180, 1:240 and 1:480) leads to costs instead of savings. For higher prior risks of CF and for the three other diseases, DNA diagnosis produces considerable savings. These results remain valid when assumptions regarding behavior, reproduction, and receiving DNA diagnosis under different circumstances are varied.

Once the population and disease rates are identified such as in the Baird model and effective cost data such as cost of counseling, cost of testing, estimated cost of lifetime treatment, etc are identified, then a researcher can move on to the mathematical model such as used in van der Reit's 1997 study to determine the cost-effectiveness of the treatment of monogenic or any congenital disease. As the medical industry continues to be driven by genomics,

such models and cost effectiveness analysis will be necessary to justify changes in procedure and policy.

Marketing & consumer issues

Much of the innovation in today's rapidly changing twenty-first century health services industry is being forced by economic considerations that are transforming the way health care is organized, delivered and financed. The world of medicine and health care can no longer afford to wait years to decide which therapies are the most efficient and cost effective. It is particularly important for health care organizations such as managed care companies and hospitals to determine the best ways to treat patients since they have declared their ability to maintain their high quality health standards in the least costly manner available. (Licinio; 2002).

At this point in time, there are seven significant market forces that are currently redefining health care as we know it. These market forces include: (1) the escalating pace of medical advancement, (2) the aging population and the Babyboomers, (3) the technological advances of the information age redefining time and space boundaries, (4) continuing economic pressures to cap expenditures and implement new insurance models, (5) the consumer revolution in which consumers are taking a more active role in their care, (6) regulatory evolution of current laws and regulations, and (7) capital constraints which cause providers to experience more and more difficulty accessing low-cost capital. While the cumulative effect of these market forces is difficult to predict with certainty, it is believed that the combination of these forces will transform

healthcare from a provider driven "seller's market" to a customer driven "buyer's market". As in existing examples of buyer's markets, the basis of competition increasingly will be to offer products and services that are better, faster, and/or less expensive than the competition (Myers, 2001). Can the promise of genomics created by the completion of the Human Genome Project lead to a solution to the future of health care that all Americans are seeking?

Explorations into the function of each human gene, a major challenge extending far into the 21st century, will shed light on how faulty genes play a role in disease causation and allow scientists to employ disease intervention. With this knowledge, commercial efforts are shifting away from diagnostics and toward developing a new generation of therapeutics based on genes. Reproductive options are being increased as genetic technologies improve and drug design is being revolutionized as researchers create new classes of medicines that target specific sites in the body and promise to have fewer side effects rather than the traditional trial-and-error method (Chanda, 2003).

Genetic testing is the highest growth segment of the diagnostics industry, with the number of new products and services far exceeding other market sectors. It is a frontier of tremendous potential for companies with the expertise to develop a fully automated platform for genetic testing. With the medical community openly voicing its approval, the healthcare industry has been forced to re-examine the benefits of genetic screening and its billion-dollar cost savings potential (genetic testing no longer cost prohibitive), helping to accelerate acceptance (Frost & Sullivan, 2001).

One evolving market subsector is gene therapy. Gene therapy offers the potential for using genes themselves to treat disease. This is one of the most exciting applications of DNA science to date. It has captured the imaginations of the public and the biomedical community for good reason. This rapidly developing field holds great potential for treating or even curing genetic and acquired diseases, using normal genes to replace or supplement a defective gene or to bolster immunity to disease (Myers, 2001).

Reproductive health is another subsector of genomics that is highly consumer driven by infertile couples with disposable income. Although the effects of assisted reproductive technologies (ART) procedures on the health and development of the resulting children are unclear to date, ART procedures such as *in vitro* fertilization (IVF), intracytoplasmic sperm injection and embryo cryopreservation, and those born after having preimplantation genetic diagnosis, are being utilized by escalating numbers and were made possible through the study of genomics. Over one million children have been born worldwide as a result of ART (GPPC, 2004).

Scientists are also working diligently to develop and perfect new birth defect detection methods. Not only do these screenings identify possible defects within embryos, but also reduce the risk of multiple births by enabling physicians to implant fewer eggs and greatly increase the probability of a successful pregnancy (Frost & Sullivan, 2001). Pre-implantation Genetic Diagnosis (PGD), also known as embryo screening, is the most common state-of-the-art procedure used in conjunction with in vitro fertilization to date. PGD was developed to

detect numerical or structural anomalies in the chromosomes of embryos, as well as conditions caused by single gene defects, but is now primarily used for gender selection in embryos for the price of approximately $20,000 per attempt. PGD is an example of a service that was developed for a specific purpose, but the consumer now dictates consumption.

Ethical, legal and social implications (ELSI)

The Human Genome Project and related initiatives, have introduced innovative techniques to revolutionize the study of genes. Genomics is laying the foundations for new approaches to the diagnosis and treatment of human disease, and introducing new possibilities for reproductive choices. This progress is accompanied by important ethical and social decisions. Although many issues are not unique to genomics (such as confidentiality, informed consent, discrimination and stigmatization, etc.), they require focused consideration in the context of genomics. Genomics is unique in that gene based approaches introduce a new language of "probability" and "susceptibility" to medical care, and provide information about participants that is often of great interest to third parties – be they families, governments, insurance companies, law enforcement or scientific researchers (WHO genomics, 2004).

Since fisal year 1991, the U.S. Human Genome Project has spent over $200 million in federal funds to help isolate genes associated with Huntington's disease, amyotrophic lateral sclerosis, neurofibromatosis types 1 and 2, myotonic dystrophy, and fragile X syndrome and to localize genes that predispose people to breast cancer, colon cancer, hypertension, diabetes, and

Alzheimer's disease. Now comes the hard part (Pellerin, 2000). Biology's 21st century megaproject starts to look relatively manageable compared to another challenge facing the enterprise: sorting out ethical, legal, and social issues associated with using this information.

Concerned about potential misuse of detailed genetic information, in 1992, NIH created the Ethical, Legal and Social Implications (ELSI) branch of the project, which receives 3% of the multimillion-dollar genome budget. The 1993 progress report introduced the most urgent research, educational, and policy issues, including developing consent and confidentiality guidelines for research with human subjects; determining a professional standard of care for delivering new genetic services; developing uniform standards governing the privacy of organs, blood, and tissues banked for clinical purposes; protecting against employment and insurance discrimination based on genetic information; and improving public understanding of the potential and limits of genetics to prevent overly deterministic readings of genetic test results that expose people to social stigma (Bezold, 2002).

Researchers also will study the eugenics movement and other social uses and misuses of genetic research, the likely priority of new genetic services in the health care system, the effects of commercialization on genetic services and research, and sociological implications of the genome project's dynamics and priorities. Lurking between the lines in the priority list are all the elements that constitute what surely will be an extended debate, not only about whether and how to use life's ultimate database but moral issues about tampering with the

natural biological process of species evolution and individual evolution (Harvey, 2002).

According to the 1991-1992 Progress Report of the National Center for Human Genome Research, ELSI aspires to develop programs that address understanding the project's ethical, legal, and social implications and to define major issues and develop policy to address them.

Knowledge gained through the genome project can be used by scientists in many ways: to unravel the pathogenesis of a disorder or understand the expression of a normal human trait, to develop clinical tests for disease or trait-specific forms of the gene, and to detect chemical-specific patterns of genetic changes. But the effects of acquiring and utilizing this knowledge create tough choices for nearly everyone (U.S. Human Genome Project, 2002).

Health professionals must decide when to offer testing, how to ensure its quality, how to interpret the results, and to whom they disclose information. Employers, insurers, the courts, and other social institutions must decide the relative value of genetic information in the decisions they make. Governments must decide how to regulate production and use of genetic tests and the resulting information and how to make testing and counseling services accessible. Society must decide how to improve public understanding of science and its social implications and increase public participation in science policy making (Pellerin, 2000).

Growing health insurance costs are prompting employers to look for ways to reduce costs like health insurance, disability insurance, lost productivity, and

training of replacement workers for skilled positions. Increased employer concerns about the costs of illness and the prospect of genetic tests that reveal a predisposition to disease are fertile ground for the use of other such tests to screen workers (Business, 2002).

Other factors may prompt insurers to use genetic tests. Once the tests become available, people can be tested privately to learn about their risks for disease. Those who are at risk are likely to buy insurance and in larger amounts. Competition among insurance companies will drive companies to genetic screening. A company that uses such tests would be able to give lower rates to those with no genetic predisposition to disease and higher rates to those at risk. People offered lower rates are more likely to buy insurance from that company, and those at risk will seek insurance from companies that do no genetic testing. These companies will either raise their rates to avoid bankruptcy or begin using genetic tests.

These are just a few of the social and legal questions raised by the availability of genetic testing. But there are medical/ethical questions as well: Is there is a need for a genome program? Are both somatic and germline therapy (somatic therapy corrects defects by adding new genes to cells but does not pass genetic changes to offspring; germline therapy passes genetic changes to future generations) medically and ethically acceptable for therapeutic but not nontherapeutic purposes? Is prenatal diagnosis ethically acceptable except where parents use it strictly for gender identification (Lindpaintner, 2003)?

The future of genomics is also surrounded by a high degree of uncertainty about its potential applications and even more about the potential of the wider social and political effects. One scenario design process utilized ten drivers of genomics as the framework for creating 4 alternative futures. The genomic drivers included social attitudes, social mobilization, demand, functionality of genomics technologies, environmental factors, regulation of genomic applications, risk, governance of knowledge, geopolitics, and business forces. For each scenario, alternative possibilities for the ten drivers were mapped out across each scenario. Justman, Bezold, and Rowley propose the following four future scenarios:

(1) Genomics gains more public acceptance as better safety standard and laws are implemented. Genomics becomes an accepted practice and many individuals use the technology to to identify their unique health risks and sensitivities.

(2) Genomics applications prove to be more difficult and expensive to develop. Public demand is reduced due to high costs. Liability lawsuits severely diminish the industry and force genomic patents into the public domain.

(3) Genomic breakthroughs accelerate and the technology is out of control. Applications are delayed in the approval process due to the mass volume of usage. Prices continue to rise due to demand combined with lack of resources.

(4) Genomics for all! Genomics is successfully implemented, with wise and participatory management of the risks and side-effects. A consensus emerges not only on how genomics should be implemented, but also the type of society that genomics should serve. Genomics plays an instrumental role in building a global society.

My hope is for the following scenario, similar to Justman, Bezold, and Rowley's scenario 4. We would live in a world where it would be possible to obtain a screening genotype at a physician's office and transmit that information to a secure database. Assisted by a decision support system, the physician would prescribe a personal immunization schedule or recommend specific preventive measures. The genotyping information would be complemented throughout the patient's life by screening programs based on molecular profiling. At any point, screening could lead to recommendations about lifestyle or nutrition, or to detection of early stages of disease. As diseases are stratified and segmented, more effective diagnosis and treatment can be designed. Unraveling the heterogeneity of disease will lead to a better understanding of individual variability in disease severity, progression, and response to therapy. Refined diagnosis and choice of personalized therapy would follow, taking into account the individual patient's genotype, history, and details of his or her molecular health profile. A pharmacogenetics approach would be utilized for drug prescription and would start with the analysis of the patient's DNA. A limited genome scan using pre-selected polymorphisms would be performed. Matching the patient's diagnosis and genome scan with drug-specific safety and efficiency

profiles would enable selection of a drug and dose optimal for the patient. Personalized therapy will be supported by an expanded spectrum of drugs developed to target particular disease subtypes on a particular genetic background (Gottweis; 2000).

Limitations

Scientists have spent a lot of effort and financial resources to understand the role of genetics in human disease and dysfunction, but a comparable effort has not been expended to understand how the environment causes impaired human health. Environmental contributions to disease are entirely preventable (Maxwell, 2001).

Critics of the HGP worry about the limitations of the project to solve environmental health problems. Critics contend that the genome project has been managed in everyway so far, but no one questioned the whole issue of whether there should be a human genome project (Pellerin, 2000). Other critics ask why we are so busy mapping the genome? These critics contend that science should be mapping the environment instead of mapping the genome. Theses critics believe we should worry about things that really make us sick. Why do scientists think it's so much easier to change genes than environmental conditions that put us at risk?

Other critics draw other lines in the sands of the genetic controversy in terms of therapeutic genetics. Biomedical ethicists distinguish between therapeutic and non-therapeutic genetic engineering. These ethicists endorse therapeutic manipulation for somatic cell and germline therapies, but reject the

use of non-therapeutic genetic engineering, which ethicists call dangerous and unfair to future generations (Maxwell, 2001).

The elimination of suffering and disease justifies decision-making on its behalf, but the situation is different. For eugenics (hereditary improvement by genetic control) or genetic enhancement, the present generation should avoid using genetic engineering to impose its own ideas about personality, intelligence, character traits, talents and the like on future generations.

Critics also describe the moral uncertainty of prenatal diagnosis as a medical practice because prenatal diagnosis is associated with selective abortion. The National Center for Human Genome Research (NCHGR) concludes that prenatal diagnosis or embryo screening (formally termed pre-implantation genetic diagnosis (PGD) analysis) is a tool parents should be able to use to make their own reproductive choices, but access to such technology should be denied parents who seek prenatal diagnosis only for purposes of gender identification. The moral framework that will guide the practice of prenatal diagnosis as a mature medical technology is still emerging. Its foundations are in the ethical traditions of clinical medicine and genetic counseling, with their complementary imperatives to enhance fetal welfare and facilitate parental choice. As the next generation of diagnostic techniques raises new moral, conceptual and social uncertainties, the relationship between the traditions will be increasingly important to the practice's moral stability (Pellerin 2000).

Finally, critics challenge the long-range safety of assisted reproductive technologies (ART). One million children have been born worldwide as a result of

ART, yet the effects of these procedures on the health and development of the resulting children is unclear. While some medical studies suggest that ART children are as healthy as their naturally conceived peers, other studies associate ART with a higher incidence of cancer, birth defects and genetic diseases. Parents and healthcare providers need access to accurate information on the health and developmental risks associated with these technologies. To assess current medical knowledge about the health and development of ART children and make recommendations for future research priorities, the Genetics and Public Policy Center has established the ART Children's Health Panel. This expert panel, co-sponsored by the American Academy of Pediatrics (AAP) and the American Society for Reproductive Medicine (ASRM), will carefully review the scientific literature and produce a report outlining its findings and recommendations (GPPC, 2003).

Public health implications

Better information on the frequency of genetic diseases existing in our population is essential for planning rational health care strategies and for estimating any possible future increase in genetic load from mutations (Baird, 1998). To initiate a nationwide intervention program for the control of any health problem, there are two prerequisites. The first is evidence that the magnitude of the problem is significant, and the second is an indication that prevention is both feasible and cost-effective (Hanan, 1997). In the case of genetic and congenital disorders, these requirements have been fulfilled.

Analysis of available epidemiological data clearly indicates that hereditary

disorders and congenital malformations are rapidly becoming a major public health concern in the North America. Moreover, great advances have been made in our knowledge of genetic disorders, and the principle of equity in health care demands that the gap between medical progress and health care services should be narrowed whenever possible (Hanan, 1997).

In an attempt to avoid or decrease the serious consequences of genetic diseases, an essential approach is to prevent the occurrence of these disorders. Various strategies have been put forward for the prevention of single-gene disorders, but none have been successful in eliminating the problem. WHO defines a control program as "an integrated strategy combining optimal patient care with prevention based on community education, prospective carrier diagnosis, genetic counseling and the offer of prenatal diagnosis". In other words, both treatment and prevention are included in the control program (WHO, 2004). A general framework for the prevention and control of genetic diseases is described below. It indicates that control and prevention can be directed at three levels, i.e. primary, secondary and tertiary; of these three, primary prevention is the most desirable (Hanan, 1997).

While the overall objective of a national program is the prevention of genetic and congenital disorders in the community, the strategies adopted to achieve this objective should be carefully selected to match the unique demographic, cultural and religious characteristics of the population and should take into consideration the priorities set and the resources available (Hanan, 1997). In all states, irrespective of the resources available, certain public health

measures capable of reducing the burden of genetic and congenital disorders can be feasibly implemented without major resource implications. (WHO, 1985). Primary prevention measures should be integrated into primary health care and include the avoidance of environmental factors implicated in producing genetic disorder and screening/carrier detection.

The environmental factors to avoid include maternal nutrition, infections and other illness, or exposure to toxic or mutagenic agents. This strategy has been most useful in primary prevention of several congenital anomalies. Maternal and paternal age also seem to play a significant role in increasing the overall incidence of chromosomal disorders, e.g. Down syndrome (Khalifa, 1999).

Screening at the population level and premarital level, followed by genetic counseling to prevent the conception of a child with a genetic abnormality in a high-risk group, defined as population of individuals with a greater opportunity to develop the disease based on genetic makeup, is one of the most effective strategies in primary prevention. One example of the application of this strategy is the control of thalassaemia by carrier screening. In Cyprus, Sardinia and the Ferrara district of north-east Italy, almost no thalassaemia major births have been reported since 1980, although the incidence was very high during the 1970s (Angastiniotis, 1981). Counseling to reduce consanguineous (descended from same parent or ancestor) marriages in high-risk families is also beneficial to prevent the birth of a child with recessively inherited disorders. Recently, preimplantation diagnosis has been introduced where the *in vitro* fertilized ovum

at the blastomere stage is tested for the suspected disease. If found to be free of the disease, then it is implanted, while if abnormal, it is discarded This approach is now applied to several diseases for which diagnosis at the gene level is standardized (El-Hazmi, 1999). Prenatal diagnosis has been carried out by fetoscopy, amniocentesis and chorionic villus sampling to detect abnor-mality in the fetus (Weather, 1991). If found to be abnormal, the pregnancy is terminated to prevent the birth of the child with a genetic disease. This strategy is used in several countries, but in the United States, the termination of pregnancy is prohibited in some states and hence such as strategy raises several ethical issues.

Secondary prevention is a strategy involving early recognition of a genetic disease and early treatment intervention to reduce the detrimental effects of a disease (WHO, 1985). Neonatal screening plays an essential role, as a child with an abnormality can be detected early and given the proper nutrition, treatment or surgical correction. It is clearly of value where the condition diagnosed is common, easily detectable, severe and treatable (El-Hazmi, 1999).

The last strategy in prevention, or tertiary prevention, involves the patient diagnosed as suffering from a genetic disease. The consequences of genetic diseases can be ameliorated and further deterioration prevented by proper management and treatment programs and rehabilitation programs (WHO, 1985). Some examples of tertiary prevention are the prevention of mental retardation in patients with phenylketonuria by the reduction of phenylalanine in their diet, and the treatment of congenital hypothyroidism by the early administration of thyroid

hormone (El-Hazmi, 1999).

To initiate interventions for the control of genetic and congenital disorders at the national level, the establishment of a vertical program for genetics is necessary. The strategies and public health approaches previously mentioned should be incorporated into the existing public health care system. Integration into reproductive health programs is probably the most appropriate way to achieve this objective. A multitude of prevention approaches can be feasibly integrated, at the primary health care level, within the reproductive health programs already operating in the United States, such as the maternal and child health care clinics and family planning clinics. Although some additional training and resources will be required, the potential benefit is considerable in terms of reduction of suffering as well as reduction of the health and economic burden related to the care of patients with genetic and congenital disorders.

In terms of NIH's ELSI program, NIH is fielding criticism aimed at the branch's failure to produce a federal genetic privacy law and at the branch's unsuitability to act as its own watchdog. Given what science knows about the history of other attempts to develop and introduce sweeping social legislation, it's not surprising that ten years into the effort, there is no federal genetic privacy law.

Such an effort is roughly equal in complexity to the human genome project itself. The criticism is less about a specific law than it is about the sense that ELSI ought to deliver some tangible products. The most visible kind of product is

a law. In the meantime, NIH's ELSI branch has delivered several policy-type products and has others in the works.

On the watchdog issue, taken up in an Office of Technology Assessment background paper released October 13, Biomedical Ethics in U.S. Public Policy. The OTA report, which concluded that the United States should have a federal bioethics body, is perceived in the scientific policy and ethics community as a first step in that effort. The formation of such a federal commission would be a step in the right direction in terms of policy recomendations. For the commission, as well as the public, the challenge will be to manage the work that comes out of the NIH genome project (Pellerin, 2000).

Based on previous recommendations from the National Action Plan on Breast Cancer (NAPBC) and the NIH-DOE Working Group on the Ethical, Legal, and Social Implications (ELSI) of human genome research, in a 1998 report the Clinton Administration announced recommendations for future legislation to ensure that discoveries made possible by the Human Genome Project are used to improve health and not to discriminate against workers or their families. These recommendations are:

(1) Employers should not require or request that employees or potential employees take a genetic test or provide genetic information as a condition of employment or benefits.

(2) Employers should not use genetic information to discriminate against, limit, segregate, or classify employees in a way that would deprive them of employment opportunities.

(3) Employers should not obtain or disclose genetic information about employees or potential employees under most circumstances. Genetic testing and the use of genetic information by employers should be permitted in the following situations to ensure workplace safety and health and to preserve research opportunities. However, in all cases where genetic information about employees is obtained, the information should be maintained in medical files that are kept separate from personnel files, treated as confidential medical records, and protected by applicable state and federal laws.

(4) An employer should be permitted to monitor employees for the effects of a particular substance found in the workplace to which continued exposure could cause genetic damage under certain circumstances. Informed consent and assurance of confidentiality should be required. In addition, employers may use the results only to identify and control adverse conditions in the workplace and to take action necessary to prevent significant risk of substantial harm to the employee or others.

(5) The statutory authority of a federal agency or contractor to promulgate regulations, enforce workplace safety and health laws, or conduct occupational or other health research should not be limited.

(6) An employer should be able to disclose genetic information for research and other purposes with the written, informed consent of the individual.

These recommendations should apply to public and private-sector employers, unions, and labor-management groups that conduct joint apprenticeship and other training programs. Employment agencies and licensing agencies that issue licenses, certificates, and other credentials required to engage in various professions and occupations also should be covered. Individuals who believe they have been subjected to workplace discrimination based on genetic information should be able to file a charge with the Equal Employment Opportunity Commission, Department of Labor, or other appropriate federal agency for investigation and resolution. The designated agency should be authorized to bring lawsuits in the federal courts to resolve issues that would not settle amicably. The courts should have the authority to halt the violations and order relief, such as hiring, promotion, back pay, and compensatory and punitive damages to the individual. Alternatively, an individual should be able to elect to bring a private lawsuit in federal or state court to obtain the same type of relief plus reasonable costs and attorney's fees. To enforce these protections, the designated enforcement agency must be given sufficient additional resources to investigate and prosecute allegations of discrimination (U.S. Human Genome Project, 2002).

In 1995, the NIH-DOE Joint Working Group on Ethical, Legal, and Social Implications of Human Genome Research and the National Action Plan on Breast Cancer (NAPBC) developed and published the following recommendations for state and federal policy makers to protect against genetic discrimination:

(1) Insurance providers should be prohibited from using genetic information or an individual's request for genetic services to deny or limit any coverage or establish eligibility, continuation, enrollment, or contribution requirements.

(2) Insurance providers should be prohibited from establishing differential rates or premium payments based on genetic information or an individual's request for genetic services.

(3) Insurance providers should be prohibited from requesting or requiring collection or disclosure of genetic information. Insurance providers and other holders of genetic information should be prohibited from releasing genetic information without the individual's prior written authorization. Written authorization should be required for each disclosure and include to whom the disclosure would be made.

Why is legislation needed now? To follow is a comprehensive list detailing the necessity:

(1) Based on genetic information, employers may try to avoid hiring workers they believe are likely to take sick leave, resign, or retire early for health reasons (creating extra costs in recruiting and training new staff), file for workers' compensation, or use healthcare benefits excessively.

(2) Some employers may seek to use genetic tests to discriminate against workers, even those who do not and may never show signs of disease--because the employers fear the cost consequences.

(3) The economic incentive to discriminate based on genetic information is likely to increase as genetic research advances and the costs of genetic testing decrease.

(4) Genetic predisposition or conditions can lead to workplace discrimination, even in cases where workers are healthy and unlikely to develop disease or where the genetic condition has no effect on the ability to perform work

(5) Given the substantial gaps in state and federal protections against employment discrimination based on genetic information, comprehensive federal legislation is needed to ensure that advances in genetic technology and research are used to address the health needs of the nation--and not to deny individuals employment opportunities and benefits. Federal legislation would establish minimum protections that could be supplemented by state laws.

(6) Insurers can still use genetic information in the individual market in decisions about coverage, enrollment, and premiums.

(7) Insurers can still require individuals to take genetic tests.

(8) Individuals are not protected from the disclosure of genetic information to insurers, plan sponsors (employers), and medical information bureaus, without their consent.

(9) Penalties in HIPAA for discrimination and disclosure violations should be strengthened in order to ensure individuals of the protections afforded by the legislation (U.S. Human Genome Project, 2002).

CHAPTER III

RECOMENDATIONS

Advances in genetic science will undoubtedly influence clinical medicine, public health, and health policy. Developing sound policy for questions related to genetic testing and counseling must take into account issues wider than the health of the patient because the consequences extend to other related individuals, as well as to society at large. As a result of the pace at which specific genes are being implicated in disease processes and drug metabolism, there is a risk that genetic testing policy could be made prematurely without conducting adequate cost-effectiveness analysis. It is important to ensure that clinical recommendations do not outpace the rate at which the effectiveness, the balance between risks and benefits, and the cost-effectiveness of genetic testing need to be rigorously evaluated (Goldie, 2001).

The further growth of genomics will also drive the funding of better surveillance systems to more accurately collect prevalence and incidence data for congenital diseases and single gene disorders. This type of health surveillance system is a necessity in the United States. With more precise disease population data, more accurate cost-effectiveness analyses can be conducted.

The sensitivity of tests for rare disorders will continue to improve as additional causative mutations are identified. Evaluating the clinical usefulness of these tests will require a careful assessment of the risks and benefits of testing; the availability of specific measures to reduce risk in genetically susceptible people will also be a major consideration (Burke, 2002).

This issue needs to be further studied as more accurate data comes available for analysis. The future has yet to be defined. It is in our hands, the hands of the patients, scientists, managers, policy makers and healthcare providers of the future.

APPENDICIES

Page

State Report Card on Testing for March of Dimes Recommended Newborn Screening Conditions

The March of Dimes recommends that every baby born in the U.S. receive, at a minimum, screening for 9 metabolic conditions plus hearing deficiency.

	Phenylketonuria	Congenital Hypothyroidism	Galactosemia	Maple Syrup Urine Disease	Homocystinuria	Biotinidase	Sickle Cell Disease	Congenital Adrenal Hyperplasia	MCAD	Hearing *
Alabama	●	●	●			●	●	●		95.0%
Alaska	●	●	●	●	●	●	●	●	●	70.0%
Arizona	●	●	●	●	●	●	●	●		95.0%
Arkansas	●	●	●				●			91.3%
California	●	●	●				●			66.0%
Colorado	●	●	●			●	●	●		97.0%
Connecticut	●	●	●	●	●	●	●	●	●	99.8%
D.C.	●	●	●	●	●		●			98.0%
Delaware	●	●	●	●	●	3	●	●	●	98.0%
Florida	●	●	●	3	3	3	●	●	3	98.0%
Georgia	●	●	●	●	●	●	●	●	3	98.0%
Hawaii	●	●	●	●	●	●	●	●	●	98.0%
Idaho	●	●	●	●	●	●	●	●	●	97.0%
Illinois	●	●	●	●	●	●	●	●	●	98.0%
Indiana	●	●	●	●	●	●	●	●	●	99.9%
Iowa	●	●	●	●	●	●	●	●	●	80.0%
Kansas	●	●	●				●			95.0%
Kentucky	●	●	●	2	2	2	●	2	2	99.5%
Louisiana	●	●	●	a	a	●	●	a	a	93.2%
Maine	●	●	●	●	●	●	●	●	●	98.0%
Maryland	●	●	●	●	●	●	●	●	●	85.2%
Massachusetts	●	●	●	●	●	●	●	●	●	99.7%
Michigan	●	●	●	●	3	●	●	●	●	95.0%
Minnesota	●	●	●	●	●	3	●	●	●	92.0%
Mississippi	●	●	●	●	●	●	●	●	●	98.0%
Missouri	●	●	●	a	a		●	●	a	97.7%
Montana	●	●	●	a	a	a	●	a	a	95.0%
Nebraska	●	●	●	a		●	●		●	97.0%
Nevada	●	●	●	●	●	●	●	●	●	97.0%
New Hampshire	●	●	●	●	●		a			90.0%
New Jersey	●	●	●	●		●	●	●	●	98.3%
New Mexico	●	●	●			●	●	●		94.0%
New York	●	●	●	●	●	●	●	●	●	96.7%
North Carolina	●	●	●	●	●		●	●	●	98.0%
North Dakota	●	●	●	●	●	●	●	●	●	92.0%
Ohio	●	●	●	●	●		●	●	●	33.0%
Oklahoma	●	●	●				●	3	3	94.0%
Oregon	●	●	●	●	●	●	●	●	●	94.0%
Pennsylvania	●	●	●	●	a	a	●	●	a	95.7%

State Report Card on Testing for March of Dimes Recommended Newborn Screening Conditions

	Phenylketonuria	Congenital Hypothyroidism	Galactosemia	Maple Syrup Urine Disease	Homocystinuria	Biotinidase	Sickle Cell Disease	Congenital Adrenal Hyperplasia	MCAD	Hearing *
Puerto Rico	●	●	●				●			no info.
Rhode Island	●	●	●	●	●	●	●	●	●	99.6%
South Carolina	●	●	●	3	3	a	●	●	●	98.1%
South Dakota	●	●	●	a	a		a		a	85.6%
Tennessee	●	●	●	●	●	●	●	●	●	90.0%
Texas	●	●	●				●	●		99.0%
Utah	●	●	●				●			98.2%
Vermont	●	●	●	●	●	●	●	●	●	95.0%
Virginia	●	●	●	●	●	●	●	●	●	99.7%
Washington	●	●	●	●	●	●	●	●	●	85.0%
West Virginia	●	●	●				●			95.0%
Wisconsin	●	●	●	●	●	●	●	●	●	95.0%
Wyoming	●	●	●			●	●	3		98.0%

Testing for all March of Dimes recommended metabolic conditions implemented

● Test authorized and implemented

* Percentage of state's newborns screened for hearing deficiency

a Selected population, pilot or supplemental program

2 Authorized but implementation contingent upon funding (in statute)

3 Authorized but not yet implemented

Sources:

National Newborn Screening and Genetic Resource Center (www.genes-r-us.uthscsa.edu) and individual state NBS laboratories

National Center for Hearing Assessment and Management (www.infanthearing.org)

Number of Disorders Included in State Newborn Screening Programs, December 2002

	Number of disorders		Number of disorders for which screening is conducted using tandem mass spectrometry (MS/MS)[a,b]	
	Screening required for all newborns	Screening conducted for selected populations, as pilot program, or by request	Screening required for all newborns	Screening conducted for selected populations, as pilot program, or by request
Alabama	5	0	0	0
Alaska	6	1	0	0
Arizona	8	0	0	0
Arkansas	4	0	0	0
California	4	28	0	28
Colorado	7	0	0	0
Connecticut	8	1	0	0
Delaware	5	0	0	0
District of Columbia	7	0	0	0
Florida	5	0	0	0
Georgia	8	0	0	0
Hawaii	7	28	0	28
Idaho	5	27	0	26
Illinois	27	0	19	0
Indiana	9	0	1	0
Iowa	6	30	1	27
Kansas	4	0	0	0
Kentucky	4	0	0	0
Louisiana	5	0	0	0
Maine	9	18	1	18
Maryland	9	0	0	0
Massachusetts	10	20	1	19
Michigan	7	0	0	0
Minnesota	5	21	0	19
Mississippi	5	0	0	0
Missouri	5	0	0	0
Montana	3	18	0	14
Nebraska	5	28	0	26
Nevada	6	0	0	0
New Hampshire	6	1	0	0
New Jersey	14	0	6	0
New Mexico	6	0	0	0
New York	10	0	1	0
North Carolina	32	0	25	0
North Dakota	4	2	0	1
Ohio	12	15	6	15
Oklahoma	4	0	0	0
Oregon	33	0	26	0

	Number of disorders		Number of disorders for which screening is conducted using tandem mass spectrometry (MS/MS)[a,b]	
	Screening required for all newborns	Screening conducted for selected populations, as pilot program, or by request	Screening required for all newborns	Screening conducted for selected populations, as pilot program, or by request
Pennsylvania	6	0	0	0
Rhode Island	9	0	1	0
South Carolina	6	0	1	0
South Dakota	3	29	0	26
Tennessee	5	0	0	0
Texas	5	0	0	0
Utah	4	0	0	0
Vermont	7	0	0	0
Virginia	8	0	0	0
Washington	4	0	0	0
West Virginia	3	1	0	0
Wisconsin	21	5	14	3
Wyoming	6	0	0	0

Source: National Newborn Screening and Genetics Resource Center websites: http://genes-r-us.uthsca edu/resources/newborn/screenstatus.htm, downloaded on January 9, 2003, and http://genes-r-us.uthsca.edu/resources/newborn/msmstests htm, downloaded on January 8, 2003

[a]States may use their own laboratory to conduct MS/MS screening or contract with other laboratories.

[b]Numbers exclude MS/MS screening for phenylketonuria, maple syrup urine disease, and homocystinuria.

Kim Lewis

From: Hyatt-Knorr, Henrietta (NIH/OD) [KnorrH@od6100m1.od.nih.gov]
Sent: Tuesday, September 14, 2004 4:08 PM
To: Kim Lewis
Cc: Genetic and Rare Diseases Info (NIH/OD)
Subject: RE: Need Rare Disease Prevalence & Incidence Data

Dear Ms. Lewis: Thanks you for your information request.

Unfortunately, there is no cohesive, single effort ongoing on collecting these data, especially since we are talking about "rare" (a prevalence in the US of under 200,000 which can mean anything from "1" to "199,999 people affected in the US). This would be prohibitively expensive undertaking, and would probably reside with CDC rather than the NIH which focuses on research and not surveillance per se. I would suggest that you search the Combined Health Information Data Base (CHID) http://chid.nih.gov/detail/detail.html (search the Medical Genetics and Rare Diseases Subfile and the Internet if needed and identify the patient support organizations web sites. Then you need to read through their materials to see if they have a prevalence estimate that fits your needs. Estimated treatment costs are just simply not available, especially since many of these conditions have a wide range of severity and, given health treatment costs, are somewhat of a moving target.

However, I am copying our Genetic and Rare Diseases Information Center. The staff may be able to give you some additional pointers or citations in the literature that estimate incidence, prevalence, or treatment cost estimates in some of the cases. Do not hesitate to contact them directly at

By Telephone
Monday - Friday, 12:00 p.m. to 6:00 p.m. Eastern Time
(888) 205-2311 (Phone)
(888) 205-3223 (TTY)

By E-mail or Fax
(Answered within 5 to 10 working days)
gardinfo@nih.gov
(240) 632-9164 (Fax)

Best regards,

Henrietta Hyatt-Knorr
Director, Policy and Program Planning and Analysis
Office of Rare Diseases, NIH
6100 Executive Boulevard, 3B01
Bethesda, MD 20892-7518
Phone: 301-435-6045
Fax: 301-480-9655
E-mail: hh70f@nih.gov
http://rarediseases.info.nih.gov/

Kim Lewis

From: Robert M. Miller [NATLFX@FragileX.org]
Sent: Tuesday, September 14, 2004 10:23 PM
To: Kim Lewis
Subject: Re: Need Prevalence/Incidence Data for Fragile X

Dear Kimberly,

Thank you for contacting the National Fragile X Foundation. A current project, funded by us, is currently under way at UC Davis in Calif., by a renowned statistician, that will answer just the questions you pose.
Unfortunately she will not be reporting her results for another six months.
In the meantime, here's what we do say:
http://www.fragilex.org/html/prevalence.htm

You may also want to visit: http://www.fpg.unc.edu/~FX/

Sincerely,

Robert Miller
Executive Director
National Fragile X Foundation
PO Box 190488
San Francisco, CA 94119-0488
USA
Tel: 800-688-8765
Fax: 925-938-9315
E-Mail: NATLFX@FragileX.org
Internet: http://www.FragileX.org

State Newborn Screening Program Fees and Expenditures Per Infant Screened

	Newborn screening fee[a]	Expenditures per infant screened[b]
Alabama	$34.00	$32.11[c]
Alaska	24.00	28.78
Arizona	20.00/20.00[d]	25.99[e]
Arkansas	14.83	17.95
California	60.00	50.85
Colorado	43.47	30.63
Connecticut	28.00	39.20
Delaware	40.69	61.28
District of Columbia	No fee	25.96
Florida	20.00	[f]
Georgia	No fee	[f]
Hawaii	27.00	26.65
Idaho	18.00	16.11
Illinois	32.00	31.00
Indiana	39.50	28.16[c]
Iowa	46.00	32.73
Kansas	No fee	17.37
Kentucky	14.50	[f]
Louisiana	18.00	25.62
Maine	33.00	34.37
Maryland	30.00	30.90[c]
Massachusetts	49.55	50.12
Michigan	42.61	25.69[c]
Minnesota	21.00	[f]
Mississippi	25.00	25.00
Missouri	25.00	26.02
Montana	36.92	48.35
Nebraska	50.00/54.60[g]	44.01
Nevada	30.00	22.96
New Hampshire	18.00	22.24
New Jersey	34.00	38.27[c]
New Mexico	32.00	31.59
New York	No fee	39.92
North Carolina	10.00	14.75
North Dakota	18.00	20.81
Ohio	33.75	21.77[c]
Oklahoma	10.50	23.43
Oregon	27.00	25.05
Pennsylvania	No fee	19.91
Rhode Island	59.00	38.52
South Carolina	21.00	38.28

	Newborn screening fee[a]	Expenditures per infant screened[b]
South Dakota	No fee	[h]
Tennessee	17.50	19.34
Texas	19.50	19.74
Utah	31.00	19.62
Vermont	27.00	27.60
Virginia	27.00	30.89
Washington	40.40	39.31
West Virginia	No fee	15.98
Wisconsin	59.50	33.35
Wyoming	No fee	16.23

Source. GAO Survey of State Newborn Screening Programs for Genetic and Metabolic Disorders, October 21, 2002

[a]We asked states to report their current fee. States responded to the survey in October and November 2002.

[b]State fiscal year 2001.

[c]State's expenditures per infant screened may not reflect a typical year because the state reported that its expenditures for state fiscal year 2001 included a significant, nonrecurring expenditure.

[d]State charges two fees, one at initial screening and another at the second screening.

[e]Expenditures include disease management and treatment services.

[f]Expenditure per infant screened not calculated because state did not report number of infants screened.

[g]Fee varies depending on laboratory conducting the screening.

[h]Expenditure information not available for state fiscal year 2001.

Kim Lewis

From: NICHD Information Resource Center (IRC) [nichdclearinghouse@mail.nih.gov]
Sent: Wednesday, September 15, 2004 11:49 AM
To: Kim Lewis
Subject: RE: Need Rare Disease Prevalence & Incidence Data

Dear Ms. Lewis:

This is in response to your inquiry to the National Institute of Child Health and Human Development Information Resource Center (NICHD IRC) regarding your request for statistical information on single gene genetic disorders in the United States, Canada and the United Kingdom.

The NICHD is part of the National Institutes of Health, a component of the U.S. Department of Health and Human Services. The NICHD has primary responsibility for conducting and supporting basic and clinical research in the biomedical, behavioral, and social sciences relating to child and maternal health, in medical rehabilitation, and in the reproductive sciences such as reproductive biology.

The NICHD IRC does not carry statistical information. You may want to contact the following organizations to see what they may be able to provide:

National Center for Health Statistics
Centers for Disease Control and Prevention
6525 Belcrest Road
Hyattsville, MD 20782-2003
Phone: (301) 458-4636
E-mail: nchsquery@cdc.gov
Web Address: http://www.cdc.gov/nchs

Communications and Public Liaison Branch National Human Genome Research Institute National Institutes of Health Building 31, Room 4B09
31 Center Drive, MSC 2152
9000 Rockville Pike
Bethesda, MD 20892-2152
Phone: (301) 402-0911
Fax: (301) 402-2218
Web Address: http://www.genome.gov

In addition, you may want to visit the National Library of Medicine's (NLM) Web site at http://www.nlm.nih.gov for information. The NLM Web site provides access to online services designed to link users to information on specific health topics. MEDLINEplus, which can be accessed directly at http://www.medlineplus.gov provides consumer information on more than 600 health topics and also contains information on prescription and over-the-counter medications, physicians, and health news. PubMed, which can be found at http://www.ncbi.nlm.nih.gov/pubmed, provides access to the NLM's searchable database, MEDLINE, which contains citations to more than 12 million journal articles. Your local university or medical school library also may be a helpful resource.

Thank you for contacting the NICHD IRC. If we can be of further assistance, please call us at
1-800-370-2943 or contact us by e-mail at NICHDInformationResourceCenter@mail.nih.gov.

Sincerely,

Chereen Leid
Information Specialist

Kim Lewis

From: .Gard (Genetic and Rare Diseases Information Center) [Gardinfo@nih.gov]
Sent: Thursday, September 16, 2004 1:19 PM
To: Kim Lewis; drpikle@msn.com
Subject: Single gene disorder prevalence and incidence data

Dear Ms. Lewis,

You recently sent an email to the Office of Rare Diseases about prevalence and incidence data for several single gene disorders. Ms. Henrietta Hyatt-Knorr responded to your request, and she copied the Genetic and Rare Diseases Information Center so that we could also suggest resources that may be helpful to you. As you do research on the Internet, you will find many resources; sometimes it may be difficult to assess their reliability and validity. At a minimum, we suggest you look at:

-- The source of the information: Is the source obvious? Does it state why it is credible? Are medical advisors associated with the site?
-- The date of the information: Does the site have a date indicating when it was last updated?

The University of Albany hosts a Web site with information and tutorials on searching the Web, Internet browsers, and research guides. Such information can help you obtain the most useful results from your searches.
http://library.albany.edu/internet/

In addition to the resources that Ms. Hyatt-Knorr suggested, you may want to continue your research by reviewing these other reliable sources.

The Genetic Alliance and the National Organization for Rare Disorders (NORD) both have searchable directories of support and lay advocacy organizations for specific disorders. These groups may be able to provide you with the statistics that you seek for some of the conditions.

To access the Genetic Alliance database, please visit the following link:
http://www.geneticalliance.org/diseaseinfo/search.asp

NORD's database is available online at the link below:
http://www.rarediseases.org/search/orgsearch.html

More information on many of these conditions can be found at the following link from MEDLINEplus, the National Library of Medicine Web site designed to help you research your health questions. Use the name of the condition of interest.
http://medlineplus.gov/

You can find more information about many of these disorders on the Genetics Home Reference website. The Genetics Home Reference: Your Guide to Understanding Genetic Conditions is a service of the U.S. National Library of Medicine. This resource provides information about genetic diseases and associated genes, a glossary of genetic terms, descriptions of genetic concepts and links to other genetic resources. To view this information, type the name of the condition in the search box and then click the link for the condition summary.
http://ghr.nlm.nih.gov/

GeneReviews is a web site that provides current, expert-authored, peer-reviewed, full-text articles describing the application of genetic testing to the diagnosis, management, and genetic counseling of patients with specific inherited conditions. Select the "GeneReviews" icon at the top of the page at the following link. Use the name of your disease of interest as your disease search term.
http://www.geneclinics.org/

You can find relevant journal articles on the conditions that you mentioned through a service called PubMed, a searchable database of medical literature. Information on finding an article and its title, authors, and publishing details is listed here. To obtain the full article, contact a medical/university library (or your local library for interlibrary

loan), or order it online using the following link. Using the name of the condition of interest as your search term should locate articles of interest. To narrow your search, click on the Limits box below the search box and specify your criteria for locating more relevant articles. For example, you can limit your search to review articles (on the pull down menu under Publication Type), articles with abstracts, only articles in English, etc.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed

The National Library of Medicine (NLM) Web site has a page for locating libraries in your area that can provide direct access to journals (print or online) or where you can get articles through interlibrary loan and Loansome Doc (an NLM document-ordering service). You can access this page at the following link.
http://nnlm.gov/members/

We hope that these links give you a good starting point in your research. We suggest that you regularly revisit the Web sites for new information that may become available in the future. Good luck on your assignment!

Sincerely,

Information Specialist

The Genetic and Rare Diseases Information Center was established by the National Human Genome Research Institute and the Office of Rare Diseases at the National Institutes of Health to provide responses to public information requests. Information Specialists are available Monday through Friday, 12:00 p.m. to 6:00 p.m. Eastern time (excluding Federal holidays), to respond to questions about genetic and rare diseases.

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Important Disclaimer:
The materials provided are for informational or educational purposes only and are not intended as a substitute for professional medical care, advice, diagnosis, or treatment. This material does not represent an endorsement of any specific tests and products by the National Human Genome Research Institute or the Office of Rare Diseases at the National Institutes of Health. We cannot guarantee the accuracy, completeness, timeliness, or usefulness of the opinions, advice, services, or other information. Moreover, we strongly recommend that you seek the advice of your health care provider with any questions regarding your medical care.

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