Phenylketonuria (PKU)

Cofactor Variants

Galactosemia

Primary Congenital Hypothyroidism

Sickle Cell Disease and Other Hemoglobinopathies

Thalassemias

Alpha Thalassemia

Beta Thalassemia

The California Newborn Screening Program

In California, the prevalence of:

PKU is 1 in 27,000 births (classical PKU only)

Approximately 15-18 cases are detected annually through the mandated Newborn Screening Program. Over 350 children have been identified with classical PKU since 1980.

Galactosemia is 1 in 73,000 births

Approximately four to eight cases are identified in California every year

Primary congenital hypothyroidism is 1 in 2,700 births

Approximately 200 cases a year are identified in California.

Sickle cell disease is about 1 per 4,400. The Newborn Screening Program detects approximately 125 cases each year.

In addition, Beta thalassemia major and hemoglobin E/Beta thalassemia are detected, occurring in about 1 in 27,000 newborns in the State.

About 5 cases of E/Beta thalassemia, 4 cases of Beta thalassemia major and 1 each of C, D and E/Beta thalassemia are identified annually.

In California the incidence of Hemoglobin H disease is about 1 in 15,000 births, or about 35 to 40 cases per year are detected.
The California Newborn Screening Program

Newborn Screening is recognized nationally as an essential preventive public health measure. All states in the nation and the District of Columbia have established newborn screening programs. The State of California began its Newborn Screening Program in 1966 with the testing for phenylketonuria (PKU). In October 1980, the program was expanded to include galactosemia, primary congenital hypothyroidism, and a more comprehensive follow-up system. In 1990, screening for sickle cell disease was added to the State's existing program. This also allowed for the identification of some of the related non-sickling hemoglobin disorders, including beta° thalassemia major, and Hb E-Beta Thalassemia. In 1999, the Program implemented screening for hemoglobin H and hemoglobin H - Constant Spring disease.

Very early detection permits the metabolic disorders PKU and galactosemia to be treated with a diet, and hypothyroidism with thyroid hormones, thus preventing the development of mental retardation and other severe health problems. Detection of sickle cell disease in newborns makes possible early entry into comprehensive care, which includes the initiation penicillin prophylaxis and parent education (e.g., identification of early warning signs and preventive health measures), factors which have been shown to reduce morbidity and mortality. Early detection of thalassemia disorders allows for close monitoring for infections and anemia. Ongoing health care and close monitoring help children with hemoglobin disorders stay as healthy as possible.

Informing Parents of the Test

State regulations (17 CCR 6500) require that prenatal care providers give pregnant women informational material about the newborn screening program. Because some women do not receive prenatal care, the same informational material. Important information for Parents about the Newborn Screening Test (IIP), is also distributed upon admission to a licensed perinatal health facility for delivery. The State Newborn Screening Program supplies copies of this pamphlet at no cost to all health professionals who serve maternity patients, to hospitals that provide maternity and/or newborn care, to local health departments, and county birth registrars.

How to Order IIP

Benefits of the Newborn Screening Program

The program screened 10,065,506 babies from October 1980 to June 2000 and identified the following disorders:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>355</td>
</tr>
<tr>
<td>Primary Congenital Hypothyroidism</td>
<td>3,236</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>132</td>
</tr>
<tr>
<td>Sickle Cell Disease* and other clinically significant Hemoglobinopathies* (Beta° Thal Major, E-Beta Thal, etc.)</td>
<td>1,229</td>
</tr>
<tr>
<td>Hemoglobin H Disease**</td>
<td>91</td>
</tr>
<tr>
<td>Total</td>
<td>5,046</td>
</tr>
</tbody>
</table>

* from 2/27/90
** from 7/96

Based on the known occurrence rates of these disorders, the number of diagnosed cases has been within the expected frequency rate. Efficient processing of test results and program monitoring have resulted in the initiation of treatment of these babies at a very early age.

Median Age of Treatment

1980 - 2000

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Age (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>10</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>5</td>
</tr>
<tr>
<td>Primary Congenital Hypothyroidism</td>
<td>9</td>
</tr>
<tr>
<td>Sickle Cell Disease*</td>
<td>55</td>
</tr>
</tbody>
</table>
The California Newborn Screening Program

High blood phenylalanine levels are indicative of one of the following categories of disorders in its metabolic pathway: classical PKU, hyperphenylalaninemia, and co-factor variant defect.

Classical PKU is an inherited recessive autosomal disorder (chromosome 12) with an incidence of 1:27,000 in California (1:15,000 in Caucasians, less common in other races). California's lower birth prevalence is due to the preponderance of non-Caucasian births. Since 1956, when PKU screening began, more than 500 cases have been detected.

The disorder is due to a lack of phenylalanine hydroxylase; this is an enzyme needed to metabolize the amino acid phenylalanine to tyrosine (another amino acid); tyrosine is a precursor for such important biochemical products as serotonin, catecholamines, thyroid hormone, and melanin. This enzyme deficiency leads to high levels of phenylalanine and low levels of tyrosine, causing:

- mental retardation
- seizures
- decreased growth rate
- poor motor skills
- hypopigmentation

Dietary restriction of phenylalanine (phe), begun within the first few weeks of life, will result in normal development. This is accomplished by replacing most dietary protein with a supplementary formula containing adequate amounts of essential amino acids other than phenylalanine. Phenylalanine can be found in all foods containing protein. By eliminating overly proteaceous foods, aspartame (NutraSweet®), and wheat products containing gluten, blood phe levels can be significantly reduced. Since phenylalanine is an essential amino acid, it should not be totally omitted from the diet: too low a phe level is not healthy, either. The recommended phe-level range is 120 to 360 mmol/L (2 to 6 mg/dl) for children.

Frequent monitoring of the blood phe level and adjustment of the diet is necessary to ensure both adequate nutrition and safe levels of phenylalanine. This strict diet should be followed indefinitely rather than discontinuing it at eight or nine years of age (which was the standard in the past). The current recommendation of diet for life was developed based on studies which indicated that maintaining low phe levels seemed to result in individuals with PKU being able to concentrate better, do better in school, and able to do more complex math problems than when they are not on a low-phe diet.

Severe mental retardation is the rule for individuals with untreated classical PKU. With early adequate treatment, mental retardation is totally preventable. If treatment is delayed for some weeks, the results are more variable. Children who are not treated until after six months of age may show some improvement in IQ, but they will be retarded. Those who are not treated until they are even older usually show little change in IQ but, a phe-restricted diet may help control seizures and/or serious behavioral problems. A mousy or musty odor in older, inadequately treated-individuals is frequently noticed.

What is primary congenital hypothyroidism?

Primary congenital hypothyroidism is an endocrine condition present at birth that occurs when the thyroid gland does not produce enough thyroid hormone to meet the body's needs. Typically, the thyroid gland makes thyroid hormones, such as thyroid (T4), which are necessary for brain and central nervous system development as well as muscle and bone growth. These hormones help to maintain body temperature and assist with intestinal movements. They also keep the chemical changes which occur in various tissues of the body going at a constant rate.

When primary congenital hypothyroidism occurs, it is usually caused by an undeveloped thyroid gland. The gland is either too small, located in the wrong place, or was never formed. An undeveloped thyroid gland either makes small amounts of thyroid hormone or none at all. If primary congenital hypothyroidism is untreated, it can lead to severe mental retardation and growth retardation. Early identification and treatment of hypothyroidism will prevent severe mental retardation and other health problems.

What are the symptoms?

The characteristic features include puffy eyes, thick tongue, coarse facial features, a hoarse cry, skin mottling (spotting of different coloring on the skin), and lethargy (extreme drowsiness or sluggishness).

What is the treatment?

The treatment requires taking a daily pill of thyroid hormone called thyroxine. You should always consult your doctor regarding any treatment recommended.
DISORDERS POTENTIALLY DETECTED

All of the disorders below are autosomal recessive, which means that, although usually neither parent is affected, each parent must have passed a gene for the disorder to their baby in order for the baby to be affected. There is a one-in-four chance that this will happen each time the couple has a birth.

**Amino Acid Disorders**

**Organic Acid Disorders**

**Fatty Acid Oxidation Disorders**

**Amino Acid Disorders**

The terms "amino acidemia" and "amino aciduria" refer to disorders in amino acid metabolism (breakdown process to provide energy or heat for body functions). Amino acids are the chemical building blocks of human proteins. Proteins are responsible for the functioning of cells in the body. In order for amino acids to work, specific enzymes must be present. Amino acid disorders result from deficiencies (lack) of enzymes needed for amino acid metabolism or transport. This results in abnormal quantities of amino acids building up in the urine or blood. In large quantities, amino acids can be toxic to the body.

Symptoms in babies will vary by disorder and may include slow development, vomiting, diarrhea, abnormal odor or color of urine and/or a build-up of acid in the body (acidosis) and can result in mental retardation.

Treatments may include replacement of the deficient enzyme, special diets and medication. Prompt treatment may prevent serious problems from developing.

- Maple syrup urine disease (MSUD)
- Homocystinuria/cystathionine beta-synthetase deficiency (CBS)
- Citrullinemia/argininosuccinic acid synthetase deficiency (ASAS)
- Argininosuccinyl-CoA lyase deficiency (ASAL)
- Phenylketonuria (PKU)
- Argininemia/arginase deficiency
- Tyrosinemia

**Organic Acid Disorders**

Organic acids are a group of chemicals that are used in critical metabolic processes of the body. Organic acid disorders usually result from a missing or malfunctioning step in amino acid breakdown (chemical breakdown) due to a lack of enzyme activity.

Symptoms will vary by disorder and may include poor feeding, vomiting, low blood sugar, drowsiness, seizures, brain disease and coma.

Treatment may include a special diet and/or medication to remedy the problems caused by the deficient enzyme activity.

- Propionic acidemia
- Methylmalonic acidemia
- Isobutyryl-CoA dehydrogenase deficiency
- Isovaleric acidemia
- 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMGCoA)
- Glutaric acidemia type-1 (GA-1)
- 2-methylbutyryl-CoA dehydrogenase deficiency
- 3-methylcrotonyl-CoA carboxylase deficiency (3MCC)
- Beta-ketothiolase deficiency (BKH)

**Fatty Acid Oxidation Disorders**

Fatty acids are a component of fat in the food we eat and from fat in our tissues. Oxidation is the process that breaks down fatty acids to release energy needed for body functions. Each step of the oxidation process is set in motion by a specific enzyme. Fatty acid oxidation disorders occur when one of these enzymes is missing.

MS/MS Parent Information

Symptoms will vary by disorder and may include drowsiness, poor tone, vomiting, low blood sugar, brain disease, liver failure, and muscle problems — all of which, without treatment, can lead to severe outcomes such as coma and death.

Treatments include low-fat diets, avoiding fasting, and maintaining a regular intake of sugar, carnitines and other supplements.

- Short chain acyl-CoA dehydrogenase (SCAD) deficiency
- Medium chain acyl-CoA dehydrogenase (MCAD) deficiency
- Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency
- 3-Hydroxy long chain acyl-CoA dehydrogenase (LCHAD) deficiency and tri-functional protein deficiency/tri-functional protein deficiency
- Carnitine palmitoyltransferase deficiency - type II (CPT-2)
- Carnitine-acylcarnitine translocase deficiency (CAT)
- Carnitine transporter deficiency
- Multiple acyl-CoA dehydrogenase deficiency (MADD)/glutaric acidemia type-2 (GA-2)
- Carnitine palmitoyltransferase deficiency - type 1 (CPT-1)

Other MS/MS topics:

**Voluntary Supplemental Testing**

**Additional Information and Resources**
Neutral Amino Acid Profile (Tandem Mass Spectrum - Neutral Loss of 102 Daltons)

- Glycine
- $^{16}$N,$^{13}$C-Glycine
- $^2$H$_4$-Alanine
- Serine
- Valine
- $^2$H$_8$-Valine
- Leucine/Isoleucine
- $^2$H$_3$-Leucine
- Methionine
- $^2$H$_3$-Methionine
- Phenylalanine
- $^2$H$_6$-Phenylalanine
- Tyrosine
- $^2$H$_4$-Tyrosine
- Glutamate
- $^2$H$_3$-Glutamate

For understanding the mass spectra presented on this page.

Key

Relative Intensity (%)
Supplemental Screening for Multiple Metabolic Disorders

MS/MS Research Project

Background

"The introduction of Tandem Mass Spectrometry (MS/MS) in the 1990’s for population-based newborn screening has enabled healthcare providers to detect an increased number of metabolic disorders in a single process using dried blood spot specimens routinely collected for newborn screening." MS/MS allows for screening of multiple metabolic disorders using a single analytical run. With this technology there is the potential to test for a wide array of metabolic disorders, including amino acid disorders, organic acidemias, and fatty acid oxidation disorders. Because the technology can detect these disorders (approximately 30 total) within 1 to 2 minutes, the system can handle the large numbers of specimens required in newborn screening. For some of the disorders identifiable via MS/MS, such as medium chain acyl-CoA dehydrogenase deficiency (MCADD), early detection and treatment can result in substantial improvements in health outcomes (i.e., prevention of mortality and improvement of quality of life). Several states have already expanded, or are in the process of expanding, their newborn screening program to add these disorders.

The California Newborn Screening Program, which has been in existence since 1980, currently tests for PKU, galactosemia, primary congenital hypothyroidism, sickle cell disease and other hemoglobinopathies. On September 28, 2000, Governor Gray Davis signed into law Assembly Bill 2427 (Kuehl) which provides for updating and expanding the newborn screening program in California. The law took effect on January 1, 2001. AB 2427 requires the Department of Health Services to investigate the feasibility of establishing a new and broader testing program, including development and evaluation of expanded genetic disease testing utilizing Tandem Mass Spectrometry. In response, the Department plans to expand screening as a part of a research (pilot) project.

The Genetic Disease Branch (GDB) of the DHS has been actively planning for implementation of the project for over a year. Meetings of metabolic and laboratory experts from across the state were held in October, 2000 and May, 2001 to develop recommendations regarding the specific disorders to be included in the initial phase and to discuss the implementation process. The research proposal for the project has been reviewed and approved by the State Health and Human Services Agency’s Committee for The Protection of Human Subjects.

This study is being conducted in part to determine which of the disorders identifiable via MS/MS meet the criteria for inclusion in California’s mandatory Newborn Screening Program, i.e., which of the unusual results have clinical significance and what warrants reporting. Initially all “interesting” or “unusual” results will be reported to the pediatric care provider, then to a metabolic specialist for evaluation. Treatment and outcome data will also be collected on all newborns referred to Metabolic Centers for follow-up.

The NBS MS/MS Research Project

The actual start date will be announced at least 1 month prior to implementation. The estimated duration of the supplemental testing is 12-18 months. Participation in the study will be voluntary and informed consent will be obtained for both the testing of specimens and for release of medical information for newborns referred to metabolic centers. There will be no additional fee charged.

for participation in the supplemental screening and no additional blood will be needed. National experience to date in MS/MS screening using a full panel of acylcarnitines and amino acid analyses has resulted in a detection rate between 1:4,000 to 1:5,000\(^2\) (Chace et al). Based on the annual California birth rate and the accept ance rate reported by other states that have offered MS/MS supplemental screening, we project about 400,000 newborns participating in the pilot project and detecting an additional 40-60 newborns with clinically significant metabolic disorders not included in the current California mandatory newborn screening program.

**MS/MS Research Project Screening Process**

Information on the mandatory newborn screening program as well as the supplemental screening via the pilot project will be provided to parents by prenatal care providers and hospital staff. Written verification of informed consent will be obtained by hospitals and birthing centers using a form provided by the State (included in the Newborn Screening Program booklet, entitled *Important Information for Parents About the Newborn Screening Test*).

Specimen collection, handling and transport will occur in the same manner as the current mandatory screening. Hospital staff will complete the demographic information on the newborn screening Test Request Form (TRF), also known as the Newborn Screening Specimen Collection Form. The blood specimen will be collected from the newborn’s heel and dropped onto the five (5) blood spots on the filter paper attached to the TRF and allowed to dry. A separate collection form for this project will not be necessary. The hospital staff will indicate whether the newborn is to be enrolled in the supplemental study by affixing color-coded stickers (indicating “YES” or “NO”) to both the demographic portion of the form and to the filter paper. They will then send the TRF with the dried blood spots to their assigned Newborn and Prenatal Screening (NAPS) Laboratories.

The NAPS Laboratories will conduct the mandatory testing as usual on all specimens deemed adequate. Data entry of demographic information will include the decision to participate in the voluntary supplemental screening. Data will be transmitted to GDB as usual. Upon completion of mandatory testing, all filter papers will be sent to the MS/MS testing laboratory, which is on site at the Genetic Disease Laboratory Section in Berkeley. The testing laboratory will run supplemental testing only on adequate specimens where informed consent has been obtained and the “YES” sticker is affixed to the form. The results of the MS/MS testing will be reviewed and released by the laboratory and then sent electronically to the Genetic Disease Branch.

Written results will be released only for specimens with unusual findings. These will be sent to the newborn’s physician and the hospital/collection site as listed on the TRF. For all unusual results the primary care provider will be contacted immediately via telephone by the MS/MS Project Clinical Follow-up Coordinator and the newborn referred to one of the California Children’s Services (CCS)-approved Metabolic Centers for confirmation of diagnosis and initiation of treatment, if warranted.

*If there is a family history of one of the conditions or other special concerns the family should be offered information on the option of obtaining supplemental testing outside of, or in addition to, the research study, e.g., optional supplemental screening is offered for a fee by Neo Gen Screening, Inc. (Bridgeville, Pennsylvania; http://www.neogenescreening.com) and Baylor University Medical Center (Dallas, Texas; http://www.baylordallas.edu).*

The evaluation component of the project will consist of: the development and maintenance of the supplemental screening database, ongoing monitoring of all aspects of the pilot project and outcome data, including analysis of laboratory data and results, collection and analysis of follow-up clinical data, collection and analysis of cost and treatment data, and assessment of which disorders would be appropriate for inclusion in the mandatory screening program. Feedback will be solicited from parents, primary care providers, CCS Centers, state staff and contractors.

**Informed Consent**

During the research project written documentation of informed consent will be required for the voluntary supplemental (MS/MS research/pilot project) testing. To help facilitate this process the information about the mandatory Newborn Screening Program and the voluntary supplemental testing have been combined into one booklet. The informed consent form, which needs to be signed at the hospital, is included in the booklet. Copies of these booklets will be distributed to hospitals and prenatal care providers one month prior to the project start date.

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\(^2\) Enhancement of Newborn Metabolic Disease Screening with the Implementation of Tandem Mass Spectrometry: Proceedings of a 2000 Workshop
Key Points About the Voluntary Supplemental Research Project:

- There is no additional cost for the voluntary supplemental screening test.
- No additional blood will be taken from the newborn.
- Knowledge gained from this project will be used to improve screening for newborns and families.
- There could be some benefit to families who participate, e.g., early detection and treatment for newborns with one of the disorders.
- Because this is a research study, written results will only be provided on specimens with unusual results. If a specimen is inadequate, the supplemental testing will not be run and parents will not be notified or offered retesting through the program.

Many current participants in the mandatory Newborn Screening Program will have the following new and/or expanded roles in this project:

**Role of Prenatal Care Providers/Birth Attendants:**
Prenatal care providers are required by law to distribute a copy of the informational material, *Important Information for Parents About the Newborn Screening Test*, which describes the mandatory newborn screening program. Prenatal care providers will need to make sure that all women who are due to deliver during the pilot period receive a copy of the revised Newborn Screening Program booklet which contains information regarding the research project and have all of their questions regarding the MS/MS research project answered.

Birth attendants will be responsible for ensuring that women who did not obtain prenatal care receive information on both the mandatory Newborn Screening Program and the MS/MS research project prior to specimen collection. They will need to verify the mother's understanding of the project and offer the option of the supplemental screening.

**Role of Hospitals/Birthing Centers**
Written verification of informed consent will be obtained by hospitals and birthing centers using the form included in the Newborn Screening Program booklet. Hospital staff will indicate whether the newborn is to be enrolled in the MS/MS research study by affixing color-coded stickers (indicating “YES” or “NO”) on the newborn screening Test Request Form (filter paper and demographic sheet). The MS/MS research project testing will only be done on initial adequate specimens with a “YES” sticker on the filter paper. Hospital staff should assure correct and accurate pediatric care provider information on the form and send the 5-blood-spot specimens on the Test Request Form via the usual Newborn Screening route to the NAPS Labs for processing.

**Role of Pediatric Care Providers**
Pediatric Care Providers should be knowledgeable about the program and available to answer questions and provide additional information to parents and hospital staff. They will need to refer patients with unusual screening results to approved CCS Metabolic Center specialists. As always, providers should not rule out metabolic disorders solely based on newborn screening results. Any signs and symptoms of potential disorders should be followed up and any diagnosed cases reported to the GDB. It is also essential that they assure that hospitals which are entering their names and addresses on the Test Request Form have accurate and current information.

Because this is a research study, written results of the MS/MS research project will only be provided on specimens with unusual findings. In these situations, the Pediatric Care Provider will be contacted via telephone by the MS/MS Follow-up Coordinator and the newborn referred to one of the California Children’s Services (CCS)-approved Metabolic Centers for confirmation of diagnosis and initiation of treatment.

**Role of Metabolic Centers**
The Metabolic Medical Specialists will be available to answer questions about the program, the MS/MS technology and the disorders being tested. They will also be asked to consult and participate in development and evaluation of the project.

The Metabolic Centers will make the arrangements for confirmatory testing and develop the diagnostic and treatment plan, which will then be forwarded to the primary care provider and the Genetic Disease Branch. Based upon experience of the research project and input from metabolic specialists, follow-up guidelines will be developed.

**Role of Local/County Health Departments**
Health Departments may be asked to locate families in their area for screening or follow up of unusual results.

**Role of NBS Area Service Center Staff**
Area Service Center Staff will contact hospitals in their regions to improve reporting of correct information on the TRF and to reinforce information provided by the State.

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3 California Code of Regulations, Title 17, Subchapter 9 Heritable Diseases, Sections 6500-6508
regarding the project. They will follow up with hospitals not offering the MS/MS research project testing or who have only a small percent of parents agreeing to participate. They may be asked to assist the MS/MS Project Follow-up Coordinator in locating a family or in dealing with a provider in their region.

Providers or patients who have questions can call the California Department of Health Services, Newborn Screening Program MS/MS Research Project Staff at (866) 718-7915 toll free for additional information.

Changes in Billing for The Newborn Screening Test

In addition to authorizing the tandem mass spectrometry research project, AB 2427 requires the Genetic Disease Branch to dramatically change the manner in which newborn screening test panels are billed. Since 1980, GDB has billed hospitals and other newborn screening providers. The providers, in turn, would bill patients, their insurance companies, and Medi-Cal. AB 2427 requires that as of July 1, 2001 GDB stop billing hospitals and other newborn screening providers. GDB will initiate direct billing for newborn screening:

1. Kaiser Permanente Health Plan will be billed directly for their patients. Kaiser patients should not receive a bill for newborn screening from GDB.

2. Medi-Cal patients will be billed directly to Medi-Cal. GDB has added a field to the demographic portion of the Newborn Screening Test Request Form (NBS-TRF) for the mother’s Medi-Cal number. GDB will use the hospital-reported Medi-Cal number to bill Medi-Cal. Those patients whose valid Medi-Cal number is reported by the hospital will not receive a bill for newborn screening from GDB.

3. The mothers of all other patients will receive a bill for newborn screening from GDB. Accompanying the bill will be an insurance information form. Mothers will have two choices. They can pay GDB directly and then submit a claim to their insurance company for reimbursement, or they can complete the insurance information form and return it to GDB. The Genetic Disease Branch will, in turn, bill their insurance company. Included with the bill, will be the telephone number that mothers can call with questions about their bill for newborn screening.

The Genetic Disease Branch anticipates sending out its first bills for newborn screening in mid-September. This means that patients whose babies were born and tested in July and August won’t receive a bill for several months after the baby’s birth. Newborns tested in July, August and September will be billed $42.00 for newborn screening. We anticipate that the cost of newborn screening will rise, for the first time since 1994, to $55.00 on or about October 1, 2001.

Newborn Screening Area Service Centers (NBS-ASCs)

| CHO | Children’s Hospital Oakland | (510) 428-3127 |
| VCH | Valley Children’s Hospital | (559) 353-6416 |
| UCLA | UCLA Medical Center | (310) 826-4458 |
| Harbor/UCLA | Harbor/UCLA Medical Center | (310) 222-3751 |
| SDICDSI | San Diego-Imperial Counties Developmental Services, Inc. | (858) 576-2975 |
| Kaiser N | Kaiser Permanente, Northern CA | (510) 752-6192 |
| Kaiser S | Kaiser Permanente, Southern CA | (626) 564-3322 |

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Sickle cell disease (sickle cell anemia, sickle hemoglobin C disease, sickle hemoglobin D disease, sickle hemoglobin E disease, and sickle beta thalassemia) is a group of hereditary disorders that affect the red blood cells. Under certain conditions, the blood cells of infants with sickle cell disease become sickle shaped, causing obstruction in the blood vessels. This leads to pain and/or damage to the tissues. The most serious problem for infants is infections, which can prove fatal. Newborns diagnosed with sickle cell disease are placed on antibiotic therapy and parents are provided information and instruction about preventive health measures as well as identification of symptoms requiring prompt medical attention. Sickle cell disease and other hemoglobinopathies are present in all population groups but are more prevalent in persons of African, Mediterranean, Asian, Southeast Asian, Caribbean, and South and Central American origins. In California, the incidence of sickle cell disease is about 1 per 4,400. The Newborn Screening Program detects approximately 120 cases each year.

What is Sickle Cell Disease?

In sickle cell disease, there is no hemoglobin A. Instead, there is only sickle hemoglobin, called hemoglobin S, or there may be hemoglobin S and another type of hemoglobin (C, D, E, or beta thalassemia). These hemoglobins cause the red blood cells to be hard and sticky, and change to a banana (“sickle”) shape. These sticky, sickled cells can clog up the small blood vessels so the blood can’t bring oxygen to the tissues. That can cause pain and damage in the area. Eventually, the sickling can affect growth and cause organ damage. The most serious problem for babies with sickle cell disease is infections. These babies can easily develop high fevers or pneumonia which require prompt treatment.

There are several types of sickle cell disease. Hemoglobin SS (also called sickle cell anemia) is the most common. Other types of sickle cell disease include hemoglobin SC disease (sickle “C” disease), hemoglobin SD or SC, and hemoglobin S beta thalassemia disease (sickle beta thal disease). Some types of sickle cell disease can cause more problems than others. For example, hemoglobin SC is often less serious than hemoglobin SS. Sickle cell disease can also affect different people in different ways, so it may be hard to know how serious it will be for a particular person.

What is the Treatment for Sickle Cell Disease?

Babies with certain types of sickle cell disease are treated with penicillin every day and get special immunizations (shots) to help prevent infections. Parents work closely with their child’s doctor, the children’s blood specialist (hematologist) and the sickle cell clinic. They learn how to care for their baby and recognize when to take the baby to the doctor to treat problems early. Good nutrition and extra fluids are very important. Sometimes hospitalization is needed for treatment with IV (medicine given through a thin tube into a vein) antibiotics and fluids. When the child is older, she may occasionally need to be given blood.

Medications to decrease or prevent sickling of the blood are being used with some patients: effectiveness and side effects are being carefully studied. For a few people with sickle cell disease, a bone marrow transplant can be done to “cure” the disease, but this is still a high-risk procedure. A new procedure called a related-donor cord blood transplant may be possible for some families with an affected child who are planning to have another child. A blood specialist can discuss all the options with the family.

What Other Hemoglobin Conditions are Detected by Newborn Screening?

There are other combinations of hemoglobin types that babies can inherit, in which there is little or no usual hemoglobin A. These conditions are uncommon, and do not cause the red blood cells to sickle. Examples of these include hemoglobin CO, hemoglobin C beta thalassemia, hemoglobin DD, hemoglobin CE, Hemoglobin DE, and hemoglobin DC. Some of these conditions cause very few problems, while others can cause health problems.
Types of Alpha Thalassemia

- Alpha thalassemia major (Hydrops Fetalis): Deletion of all four alpha globin genes. No alpha chains, which are necessary for the formation of fetal hemoglobin, are produced. Death usually occurs in utero or early infancy. Treatment consists of ongoing transfusions.

- Hemoglobin H (Hb H) disease: Deletion of three alpha globin genes. The clinical complications associated with Hb H disease are variable. This generally results in mild to moderate anemia, and is often associated with macrocytosis, hypochromia, and red cell fragmentation.

Hemoglobin H is an abnormal hemoglobin found in people with alpha thalassemia. When three or more alpha globin genes fail, there is an excess of beta globin chains. The excess chains create unstable tetramers called hemoglobin H. The tetramer of beta globin chains forms when there are insufficient alpha (α) chains to make normal adult hemoglobin (HbA). The fetus manufactures gamma (γ) chains rather than β chains, and the tetramer of γ chains that forms is called hemoglobin Bart's (Hb Bart's). During the newborn period, when gamma globin production is still high and beta globin production is low, the gamma chains form the unstable tetramers identified as hemoglobin Bart's. However, Hb Bart's decreases with the normal decrease in gamma chain production and therefore, over time, it disappears and is replaced by Hb H. These unstable tetramers eventually precipitate in the red blood cells, causing membrane damage and premature destruction of the cells producing a chronic hemolytic anemia. It is the identification of large amounts of Hb Bart's that leads us to presume the infant will have Hb H disease. DNA testing is necessary to make the final diagnosis.

- Hemoglobin H (Hb H)-Constant Spring disease: Deletion of two alpha globin genes and a point mutation of a third. This is generally a more severe form of Hb H disease, usually with a moderate to severe clinical course. Complications include the development of splenomegaly and cholelithiasis. Some individuals may require intermittent to chronic transfusions.

Clinical symptoms for both forms of Hb H disease that can begin at birth include pallor and jaundice. In addition, severe anemia may be caused by certain types of medications (including some antibiotics) as well as fava beans and mothballs. Avoidance of these substances is recommended. Detailed list of substances to avoid.

- Alpha thalassemia trait (also called alpha thalassemia minor): Deletion of two alpha globin genes. This condition is clinically benign. The clinical manifestations include microcytosis and mild, if any, anemia, which is often confused with iron deficiency anemia. However, as the individual also has iron deficiency anemia, iron supplementation is usually not recommended. People with alpha thalassemia trait may be at risk for having a child with hemoglobin H disease or alpha thalassemia major.

- Alpha thalassemia "silent carrier": Deletion of one alpha globin gene. This condition is clinically benign, usually with no clinical manifestations.

What is the Treatment for Hemoglobin H Disease?

The child's doctor or blood specialist should be notified whenever the child becomes ill, so any infection can be promptly treated. If the anemia becomes severe, the child may need a blood transfusion. The doctor will discuss which medications to avoid. Extra amounts of a vitamin called folic acid may be given to the child. Parents should not have mothballs or fava beans in the home. The blood specialist will discuss how to care for the child, and what symptoms of severe anemia to watch for. Most people with hemoglobin H disease can lead relatively normal lives with proper treatment.

What is Beta Thalassemia Disease?

Beta thalassemia disease is also called beta thalassemia major, Mediterranean Anemia, or Cooley's Anemia (Dr. Thomas Cooley first described this disorder). In beta thalassemia disease, the child inherits a gene for beta thalassemia from each parent. There is an absent or decreased amount of one of the components of hemoglobin, the beta globin chains. This causes very little or no normal hemoglobin to be made. The red blood cells break down, and there is severe anemia. Without treatment, there is pallor, weakness, and poor growth. The liver and spleen can become enlarged, and changes in the bones can happen as they try to make more red blood cells. Without treatment, the heart fails, causing death.

Some types of beta thalassemia disease can be less severe, requiring less frequent treatment (these types may be called "beta thalassemia intermedia").

What is the Treatment for Beta Thalassemia Disease?

If the anemia is severe, the child will need regular blood transfusions, beginning as early as six weeks of age. Most transfusions are done once or twice a month. The child will also need medicine to remove the extra iron that builds up in the body as the red blood cells break down. There is more susceptibility to infections. Children with less severe anemia may receive less frequent transfusions, or may need them only occasionally.

For some children with beta thalassemia major, bone marrow transplants can be done if there is a well-matched donor. A successful transplant could cure the disease, however, it is still a high-risk procedure. A new procedure called related-donor cord blood transplant may be possible for families with an affected child who are planning to have another child. Some medications that could increase the amount of hemoglobin in the blood are being studied. The baby's blood specialist can discuss all the options with the family.

What is Hemoglobin E?

Hemoglobin E is a very common type of hemoglobin in Southeast Asians and in Californians of Southeast Asian origin. Newborn Screening in California detects hemoglobin E, without any of the usual hemoglobin A, in many babies every year. The test results for newborns with Hb EE and Hb E B that look the same. Hb EE is not a disease, but Hb E B that can be clinically significant. Repeat testing, which is part of the NBS Program, is required to distinguish between the two. Repeat testing most often will show that the baby has hemoglobin E B, which is not a disease, and does not require treatment. There is a mild anemia that is not helped by taking iron. The doctor should test for the amount of iron in the child's blood before giving the child extra iron.

Sometimes, further testing will show that the baby inherited a gene for hemoglobin E from one parent, and a gene for beta thalassemia from the other parent. In this case, the baby has a hemoglobin disease called hemoglobin E beta thalassemia disease. Effects of this disease range from mild to severe anemia and causes problems similar to beta thalassemia disease (see section above).

What is the Treatment for Hemoglobin E Beta Thalassemia Disease?

When the anemia is severe, the child will need regular blood transfusions, as in beta thalassemia disease. (See "What is the Treatment for Beta Thalassemia Disease?" above.)
Fig. 7.32. Chromosomal location (16p) and organization of the human α globin gene cluster. ψ, pseudogene; IVS, Introns (intervening sequences, white boxes). The numbers underneath the Hb α' gene 31, 32, 99, 100 ... refer to the codon numbers of the sequence at which a given intron interrupts the exon sequence. Intron 1 is interspersed between codon 31 and 32. (Only one pseudogene for Hb α is shown; newly discovered pseudogene 3' of Hb α, is not shown) (Updated Antonarakis et al., 1985 [12])

Fig. 7.33. Chromosomal location (11p) and organization of the human β globin gene cluster. Symbols and explanation identical as for Fig. 7.32 [12]

**FIGURE 3.49** The α₂β₂ tetramer of human hemoglobin. The structure of the two identical α subunits (red) is similar to but not identical with that of the two identical β subunits (yellow). The molecule contains four heme groups (black with the iron atom shown in purple).
Table 7.15. Clinically important hemoglobinopathies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetics</th>
<th>Clinical severity</th>
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<tbody>
<tr>
<td>Sickle cell syndromes</td>
<td></td>
<td></td>
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<tr>
<td>Sickle cell anemia</td>
<td>Homozygote for Hbs</td>
<td>+ + +</td>
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<tr>
<td>Sickle β-thal disease</td>
<td>Compound heterozygote for Hbs and β-thal</td>
<td>+ to + ++</td>
</tr>
<tr>
<td>Sickle Hb C disease</td>
<td>Compound heterozygote for Hbs and HbC</td>
<td>+ to +</td>
</tr>
<tr>
<td>Sickle cell trait</td>
<td>Heterozygote for Hbs</td>
<td>0</td>
</tr>
<tr>
<td>α Thalassemias</td>
<td></td>
<td></td>
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<tr>
<td>Hydrops fetalis</td>
<td>4 Hb α deletions</td>
<td>Lethal</td>
</tr>
<tr>
<td>Hβ H disease</td>
<td>3 Hb α deletions (or 2 Hb α deletions and heterozygote for Hb CoSp) or point mutation</td>
<td>+ +</td>
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<tr>
<td>α-thal-1 heterozygote</td>
<td>2 Hb α deletions or point mutation</td>
<td>+</td>
</tr>
<tr>
<td>α-thal-2 heterozygote</td>
<td>1 Hb α deletion or point mutation</td>
<td>0</td>
</tr>
<tr>
<td>Hb Constant Spring (CoSp)</td>
<td>α Chain terminus mutant</td>
<td>+</td>
</tr>
<tr>
<td>β Thalassemia</td>
<td></td>
<td></td>
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<tr>
<td>β^0 (thalassemia major or Cooley anemia)</td>
<td>Homozygote</td>
<td>+ + +</td>
</tr>
<tr>
<td>β^0-thal major (Cooley anemia)</td>
<td></td>
<td>+ + to + + + + +</td>
</tr>
<tr>
<td>β^0/β^+ thalasemia</td>
<td>Compound heterozygote</td>
<td>+ to + + + +</td>
</tr>
<tr>
<td>Hb Lepore heterozygote</td>
<td>δ^0-β^+ fusion</td>
<td>(+ + + +) (for heterozygotes)</td>
</tr>
<tr>
<td>β^0, β^+ and δβ^0-thal trait</td>
<td>Heterozygous</td>
<td>+</td>
</tr>
<tr>
<td>HbE-β-thal</td>
<td>Compound heterozygotes</td>
<td>+ + +</td>
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<tr>
<td>Unstable hemoglobin diseases</td>
<td>Congenital nonspherocytic hemolytic anemia of Heinz body type</td>
<td>Heterozygous – dominant (many different varieties)</td>
</tr>
<tr>
<td>Hemoglobinins with abnormal oxygen affinity</td>
<td>Familial erythrocytosis (high affinity)</td>
<td>Heterozygote-dominant (many varieties)</td>
</tr>
<tr>
<td>M hemoglobin</td>
<td>Familial cyanosis (methemoglobinemia)</td>
<td>Heterozygote-dominant (3 varieties)</td>
</tr>
</tbody>
</table>

* Milder diseases in β-thal^+ homozygotes of African origin.

Fig. 7.48. Peripheral blood smears of a normal individual (A), of patients with heterozygous β thalassemia (B), of heterozygous α-thal-1 (C), and of β thalassemia major (D). (From Bunn et al. 1977 [421])
**Thalassemia vs. Sickle Cell**

Thalassemia eliminates or reduces a globin chain — α or β.

**Figure 21.7** Diagnosis of β-thalassemia caused by a partial deletion of the β-globin gene. The family pedigree is shown positioned above each individual's genotype on a Southern blot. The normal β-globin gene (β⁺) contains three exons and two introns. The deleted β-globin gene (β⁻) has the third exon deleted. Arrows indicate the cutting sites for restriction enzymes used in this analysis. The normal gene produces a larger fragment (shown as the top row of fragments on the Southern blot); the smaller fragments produced by the deleted gene are represented at the bottom of the gel. The genotype of each individual in the pedigree can be determined from the pattern of bands on the blot, and these are shown below the blot.

**Sickle Cell Changes the β-globin protein but does not decrease its amount**

**Figure 21.8** Southern blot diagnosis of sickle-cell anemia. Arrows represent the location of restriction enzyme cutting sites. In the mutant (β⁻) globin gene, a point mutation (GAG → GTG) has destroyed a restriction enzyme cutting site, resulting in a single large fragment on a Southern blot. In the pedigree, the family has one unaffected homozygous normal daughter (II-1), an affected son (II-2), and an unaffected fetus (II-3). The genotype of each family member can be read directly from the blot, and these are shown below the blot.
Medical Care & Health Promotion

Child/Adult Testing and Screening

1. Diagnostic process to determine whether a person has late onset genetic disease, contain genetic disease, or to determine if person susceptible to cancer, hypertension, high cholesterol, etc. In order to take preventive action.

2. Cannot make mandatory - personal autonomy.


3. Main issues - Access voluntarily to all tests for liability.
   a. Legal duty of physicians to inform patients of availability of test results - If test reliable - then standard of care, test law is applicable.
   b. Physician has liability if patient's interest in needing test not considered.

4. Cost barriers; Universal Access; Health Insurance pays for tests.

Genetic testing of children implicates important concerns about individual autonomy and the interest of the patients. Before testing of children can be performed, there must be some potential benefit from the testing that can reasonably be viewed as outweighing the disadvantages of testing, particularly the harm from abrogating the children's future choice in knowing their genetic status. When there is such a potential benefit, parents should decide whether their children will undergo testing. If parents unreasonably request or refuse testing of their child, physician should take steps to change or, if necessary, use legal means to override the parents' choice. Applying these principles to specific circumstances yields the following conclusions:

(1) When a child is at risk for a genetic condition for which preventive or other therapeutic measures are available, genetic testing should be offered or, in some cases, required.

(2) When a child is at risk for a genetic condition with pediatric onset for which preventive or other therapeutic measures are not available, parents generally should have discretion to decide about genetic testing.

(3) When a child is at risk for a genetic condition with adult onset for which preventive or other therapeutic measures are not available, genetic testing of children generally should not be undertaken. Families should still be informed of the existence of tests and given the opportunity to discuss the reasons why the tests are generally not offered for children.

(4) Genetic testing for carrier status should be deferred until either the child reaches maturity, the child needs to make reproductive decisions or, in the case of children too immature to make their own reproductive decisions, reproductive decisions need to be made for the child.

(5) Genetic testing of children for the benefit of a family member should not be performed unless the testing is necessary to prevent substantial harm to the family member.

When a child's genetic status is determined incidentally, the information should be retained by the physician and entered into the patient record. Discussion of the existence of this finding should then be taken up when the child reaches maturity or needs to make reproductive decisions, so that the individual can decide whether to request disclosure of the information. It is important that physicians be consistent in disclosing both positive and negative results in the same way since if physicians raise the existence of the testing results only when the results are positive, individuals will know what the results must be. This information should not be disclosed to third parties. Genetic information should be maintained in a separate portion of the medical record to prevent mistaken disclosure.

When a child is being considered for adoption, the guidelines for genetic testing should be the same as for other children.
Genetic Testing Procedures

Prior to Birth

DNA-Based Diagnosis of Genetic Diseases

DNA only!

Figure 27.1
Amniocentesis and chorionic villus sampling. (a) A sample of amniotic fluid (mostly fetal urine and other secretions) is taken by inserting a needle into the amniotic cavity during or around the sixteenth week of gestation. The fetal cells are separated from the fluid by centrifugation. The cells can be used immediately, or more usually they are cultured so that a number of biochemical, enzymatic, and chromosomal analyses can be made. The cultured cells can also be a source of DNA. (b) Chorionic villus sampling is performed between the eighth and twelfth weeks of gestation. A catheter is introduced through the vagina or transabdominally, and a small sample of chorionic villi is drawn into the syringe. DNA can be isolated directly from the tissue, or cell cultures can be established. Note that the various elements of this figure are not drawn to scale.
Social and Ethical Issues Surrounding Preimplantation Embryo Diagnosis

1. In 1990, Germany passed a law that prohibits preimplantation embryo testing.

2. A 1993 report from Canada’s Commission on Reproductive Technologies warns against allowing market forces to determine the use of reproductive technologies. It also calls for creation of a permanent regulatory and licensing body to govern all aspects of the new reproductive practices, including sperm banks and in vitro fertilization.

3. In 1994, France and Norway passed legislation that limits genetic testing to situations in which the results are medically therapeutic, and authorizes governmental bodies to establish the criteria for defining “therapeutic” in this context. These laws prohibit the use of genetic testing for sex selection and normal trait enhancement.

4. In 1994, a U.S. National Institutes of Health advisory panel issued guidelines for federally funded research on embryos. These guidelines allow the use of preimplantation embryo testing for disease diagnosis and accept the practice of determining an embryo’s gender to diagnose a sex-linked disease, such as hemophilia A. The guidelines do not accept sex selection for any other reason. An oversight committee would monitor compliance with the guidelines to ensure the scientific qualifications of federally funded researchers as well as the likelihood that their studies will produce “significant scientific or clinical benefit” that cannot be “otherwise accomplished by using animals or unfertilized gametes.”

At the same time, the United States had more than 300 privately run, unregulated in vitro fertilization clinics, commonly referred to as IVF Centers. Most of these centers were willing to do whatever a paying client requested, including sex selection and analysis of the genetic susceptibility for complex traits whose inheritance is not yet well understood.

This range of responses to the issues generated by the new reproductive technologies shows a diversity of approaches based on national culture and history. It also reflects international apprehension about the potential for misuse and abuse of the new technologies. Here are some of the main concerns.

1. **When Should the Tests Be Used?**
The couple in our opening story whose firstborn suffered from cystic fibrosis faced a medical problem. Preimplantation diagnosis could help them have a second child unaffected by the disease. With no cure at present for CF and no therapy that allows CF-affected people to look forward to a life of normal length, this is an example of medically therapeutic testing. Most governmental committees and bodies argue against testing for any other reason, but commercial clinics do not. Moreover, if postnatal therapies for cystic fibrosis, such as nasal sprays that introduce a normal CFTR protein into the respiratory tissues or protocols that insert normal CF genes in the cells of the lungs and nasal passages, become available, some medical practitioners may no longer consider preimplantation diagnosis a preferred therapy.

2. **How Should the Tests Be Carried Out?**
The couple in our opening story began by consulting a genetic counselor and then worked with medical practitioners associated with a university laboratory. Most geneticists agree that counseling before a procedure should foster an open discussion of all the issues (including the possibility that the tests might give false negatives); and that long-term follow-up should be part of the process. The preimplantation testing itself, like other forms of genetic testing, should be carried out by highly trained personnel in licensed laboratories. These accredited laboratories operate according to professional standards and have scientific and ethical review boards that monitor all work.

3. **Who Should Have Access to the Technology?**
The combination of in vitro fertilization and preimplantation testing cost $6000 to $10,000 in 1994. Should the government provide tests for people who cannot afford them? How should society decide this issue? (A related discussion of access to medical technology appears in the Genetics and Society box in Chapter 1.)

4. **Should Parents Have the Right to Make Any Genetic Decision?**
If, for instance, they decide to have a child affected by a genetic disease, should they bear all financial responsibility for its care, or should some form of universal health insurance provide help?

5. **Who Should Have Access to Test Results?**
Just the parents? The parents and eventually the child? The parents, the child, and certain community institutions, such as schools? Some combination of these plus commercial enterprises such as insurance companies and places of employment? (We discuss this same question of privacy in relation to other types of genetic testing in the Genetics and Society boxes in Chapters 1 and 2.)

6. **What Constitutes a Human Individual?**
Cultural and religious beliefs, rather than scientific knowledge and social customs, are the basis for answers to this question. Some people see preimplantation diagnosis as an alternative to abortion that allows a couple to make a decision before pregnancy, and thus a life, begins. Others argue that even at the eight-cell stage, a preimplantation embryo is the equivalent of a human being, and rejection of an embryo is the equivalent of killing a human being.

Although there are no simple solutions to these complex issues, geneticists around the world agree on the need for continuous discussion and tight oversight of the development of the new reproductive technologies.

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Family Planning and Reproductive Issues

1. Major Impact - Hundreds of genetic disease genes can be screened for using SAGE (PCR), amniocentesis, or chorionic villi testing. Parental/family testing - With Human Genome Sequence - All disease genes can be tested for!!! Can determine whether parents are carriers for embryo, fetus, child has genetic disease!

2. Remember - 1 in 2% of all live births have genetic defect due to a mutation in a disease gene! And we all carry a few deleterious gene alleles!

3. Legal Issues Controversial
   a. abortion debate/embryo rights
   b. women's rights/reproductive choice
   c. eugenic concerns
   d. genetic engineering of human cells

4. Ethically and Legal Presumption of Voluntary Choice for Reproductive Matters - Voluntary Testing of Women's Right to Reproductive Choice -
   a. voluntary testing
   b. Griswold vs. Connecticut + Roe vs. Wade (contraception/abortion) "right to privacy" is conceptualized as a substantive 5th/14th amendment liberty - procreative choice is hedged by a substantive liberty
Main legal issue - Tort liability

a. Gain access to knowledge & act on it by contraception, embryo testing, pre-natal testing, for abortion

b. Tort law states that couples have the right to avoid birth of handicapped children if tests or procedures to avoid birth are available

c. Wrongful birth/life cases

(1) Scurfield vs. Bio-Science Laboratories (CA)
   Child/parent's can bring tort suit against a lab that failed to carry out Tay-Sachs test properly, giving birth to child - legal tort liability

(2) Goodin vs. Goodin (NY)
   Court held that boy can sue mother for causing his teeth to be brown because she took tetracycline during pregnancy!

Several states have now enacted statutes prohibiting wrongful birth suits against parents by children - CA - Terpin vs. Sortini - "purpose to eliminate any liability on other economic message which might induce parents to abort or conceive a potentially defective child"
"Wrongful-Birth" Lawsuits Abolished in Georgia and In Michigan

By Liz Townsend

Courts in Michigan and Georgia have rejected attempts by parents of disabled children to sue doctors who, the parents claimed, failed to discover their babies' birth defects in time for an abortion.

The Michigan Court of Appeals and the Georgia Supreme Court ruled that these "wrongful-birth" lawsuits are invalid under state law. The Michigan appeals court warned that such suits "could quickly slide into applied eugenics and the elimination of supposedly unfit lives," while Georgia's high court held that state law "does not recognize a cause of action for wrongful birth."

Wrongful-birth lawsuits remain legal in 27 states. Doctors such as James Delahunty of New Jersey, founder of the Association of Pro-Life Obstetricians and Gynecologists, have lost suits that claimed they refused or neglected to offer amniocentesis or other diagnostic tests that could have identified babies' disabilities to pregnant women.

Last March Delahunty was ordered to pay $1.85 million to the parents of Michael Imber-gamo, a four-year-old little boy with Down syndrome. Michael's parents testified that they would have aborted him if they had discovered his condition before birth, the Washington Times reported.

"Some women want to kill their children because they are handicapped," said Delahunty, according to the Times. "If genetic tests give them wrong results, they blame the doctor. I was blamed."

Delahunty's lawyer said that wrongful-birth lawsuits are a product of technology that can more easily identify disabilities in unborn children. "Patients who had disabled children in the past didn't think of suing the doctor," Tom Chamsky told the Times. "But as technology has grown, some women think that their child's disability is someone else's fault."

Both the Georgia and Michigan cases concerned babies whose disabilities were not identified by doctors from ultrasound tests.

The Georgia case involved the son of Andrew and Jennifer Eitkind, who was born with Down syndrome in September 1995. According to the Georgia Supreme Court's July 8 decision, Dr. Ramon Suarez told Jennifer Eitkind (who is also a doctor) that her baby "was developing normally and that she was not at risk for birth defects" after two ultrasounds and a blood test, and advised against the more invasive amniocentesis procedure. Dr. Eitkind did not have an amniocentesis.

After their son was born with Down syndrome and a malformed heart, the Eitkinds sued Suarez. According to the court decision, the Eitkinds asserted that "but for the treatment or advice provided by the defendant, [they] would have aborted the fetus, thereby preventing the birth." The Eitkinds sought to have Suarez pay for the costs of raising their son, the Atlanta Journal-Constitution reported.

The Georgia Supreme Court had previously abolished wrongful-birth lawsuits in the 1990 Atlanta Obstetrics & Gynecology Group v. Abelson decision. The Eitkinds asked the court to overturn Abelson on several grounds, including constitutional and due process concerns. However, the court, by a 6-1 majority, rejected all their arguments, ruling that "Georgia tort law does not recognize a cause of action for wrongful birth."

The Eitkinds' main contention was that Dr. Suarez's failure to identify the baby's Down syndrome "interfered with their choice of whether to have an abortion" and that the ban on wrongful-birth suits also stems in the way of the abortion "right," according to the court decision.

However, the court insisted, "refusal to recognize wrongful birth, absent authorizing legislation, does not interfere with Dr. Eitkind's constitutional right to an abortion."

In a strongly worded decision, the Michigan Court of Appeals rejected the lawsuit brought by the parents of four-year-old Shelby Taylor, who sued Dr. Surender Kumpati for finding "no visible abnormalities" in a December 4, 1993, ultrasound.

According to the June 25 appeals court decision, Shelby was born on April 19, 1994, with a "missing right shoulder, fusion of left elbow, missing digits on left hand, missing femur on left leg and short femur on right," according to the court. Her parents contended that "the failure to reveal the disabilities deprived the Taylors of their right to make a reproductive decision regarding the pregnancy," according to the court decision. They also alleged that Kumpati was liable for the "emotional distress" they suffered when their little girl was born.

Overturning prior decisions that had allowed such lawsuits, the Court of Appeals rejected the Taylors' arguments and ruled that wrongful-birth suits are not valid under state law. The court saw much danger in the theory behind these suits, that parents should be compensated if they were not able to abort a disabled child.

"The very phrase 'wrongful birth' suggests that the birth of the disabled child was wrong and should have been prevented," Judge J. Whitbeck wrote for the 2-1 majority. "If one accepts the premise that the birth of one 'defective' child should have been prevented, then it is but a short step to accepting the premise that the births of classes of 'defective' children should be similarly prevented, not just for the benefit of the parents but also for the benefit of society as a whole through the protection of 'public welfare.' This is the operating principle of eugenics."

The court also rejected the argument that wrongful-birth lawsuits are required to ensure the "right" to abortion that was legalized in Roe v. Wade. Whitbeck wrote that Roe allows the "state to make a value judgment favoring childbirth over abortion." For example, previous courts have found that the Michigan Constitution does not require the state to fund abortions, but Michigan does provide financial support for childbirth.

"As the state has no obligation to affirmatively aid a woman in obtaining an elective abortion by paying for it," Whitbeck wrote, "the state similarly has no obligation to take the affirmative step of imposing a civil liability on a party for failing to provide a pregnant woman with information that would make her more likely to have an elective, and eugenic, abortion."

The Michigan decision called attention to the "slippery slope" that is evident in wrongful-birth lawsuits, a slope that pro-lifers have been warning about for years. "[I]f it is but another short half step from the concept of preventing the birth of an 'unfit' or 'defective' child proposing, for the benefit of the child's overburdened parents and of society as a whole, that the existence of the child should not be allowed to continue," Whitbeck wrote.

"After all, if that child never should have been born, then that child has no real right to go on living, thereby imposing the costs of the child's continued existence upon the parents and society. This, we conclude, is the logical end of the slippery slope inherent in the application of the benefits rule through the wrongful birth tort."

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5. **Mandatory Testing**

a. Would violate right to bodily integrity!

b. Tort law require that person be informed that tests are available to screen for carrier status. But tests

c. **Key Questions?**

1. Do people have an obligation to reproduce "reasonably" or not impose undue burdens on offspring or society? Who pays?

2. Is it possible/desirable to reduce births of children with genetic diseases? If can be prevented by testing (e.g., Down's) by genetics?
Genetic Testing Discussion Scenario

Scenario A : Having Children: Exploring the Options
Scenario B : Prenatal Genetic Testing
Scenario C : Selecting for Genetic Traits

Introduction

Welcome to the Discussion Scenarios. The five scenarios in this section present many of the ethical issues that come up in connection with some uses of biotechnology. You've entered a discussion about: genetic testing.

You are about to read a series of short stories. The stories are fictitious, but we hope the situations we describe and the questions we raise will help you consider different points of view on the ethical issues associated with genetic testing. The questions aren't necessarily intended to lead you to a set of answers. The purpose is to encourage you to think about the issues from a variety of perspectives.

These Discussion Scenarios may not address all the ethical issues or concerns related to genetic testing. We also recognize that we may not have asked all the 'appropriate' questions to help bring the issues to light or that are of importance to you, and realize that no choice of questions can be truly 'ethically neutral.'

This is why the questions are intended as a starting point for a broader look at the issues associated with genetic testing. We'll be revising the questions over time, so we encourage you to get back to us with new issues that you consider important.

Elsewhere in this web site, in the section called Whose Values? Who Decides?, we talk about the difference between individual and societal ethics. There are many situations where what we want as individuals may not be the same as what we expect our government to do. As you read the Discussion Scenarios, think about which questions in the stories should be left to the individuals or companies to decide, and which ones should be answered by society as a whole. We also look at two different philosophical viewpoints that underlie ethical decisions. In one of these traditions, decisions are evaluated based on their consequences. In the other, choices are based on
a set of principles, regardless of the consequences. As you read each story, think about how these philosophical approaches and other kinds of information can help you reach your own conclusions on the ethics of genetic testing.

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**Scenario A: Having Children; Exploring the Options**

Faye and Michael want to start a family. But they know that both of their families have a history of *Tay-Sachs Disease*, an incurable condition that leads to deterioration in a person's brain. Children born with Tay-Sachs usually lose their eyesight after about a year, and rarely live beyond the age of five.  

Knowing that a person can carry Tay-Sachs without getting it, Michael and Faye asked their doctor for *genetic testing* first to determine if they are carriers and second to find out whether their future children might be at risk. Based on blood sampling, they found out that they were both carriers, meaning that a child they conceived naturally would have a one in four chance of being born with the disease.

Faye and Michael must now decide whether to conceive a child naturally, adopt a child, not have children at all or request pre-implantation genetic diagnosis (PGD). PGD is a relatively new technology where a number of Faye’s eggs are fertilized by Michael’s sperm in a laboratory. Genetic testing identifies the embryos that are most likely to be Tay-Sachs carriers, or to acquire the disease, and those embryos are not reimplanted in Faye’s womb.

**Discussion Questions**

1. If Faye and Michael decide to have a child, they want to do everything they can to make sure the child is not born with Tay-Sachs, since they believe this would be a very painful experience for the child, and for themselves. Is this a reasonable decision to make? Why or why not?

Here are some of the alternatives available to Faye and Michael if they decide they want a child:

- They could conceive the child naturally, but terminate the pregnancy if a prenatal genetic test shows that the fetus has Tay-Sachs. The couple would have a choice of two tests chorionic villus sampling, which takes place after 10 to 12 weeks of development, or amniocentesis, which is carried out after 16 weeks of development. Both tests carry a risk of miscarriage, in the range of 1 in 500. The risk may be slightly higher for chorionic villus sampling.

- Another option is to use the relatively new technology of pre-implantation genetic diagnosis (PGD), where a number of Faye’s eggs are fertilized by Michael’s sperm in a laboratory. Genetic testing identifies the embryos that are most likely to be Tay-Sachs carriers, or to acquire the disease, and those embryos are not reimplanted in Faye’s womb.
This type of genetic testing takes place at a much earlier stage, and avoids the risk of miscarriage or harm to the fetus that can occur with amniocentesis or chorionic villus sampling. But the in vitro fertilization technique that accompanies the test has other drawbacks. Only one in four implanted embryos results in a pregnancy, and some women experience side-effects from the fertility drugs they have to take during in vitro fertilization. The process is very expensive, is usually paid for by the couple, and is not currently available in all Canadian cities.

- The couple could adopt, knowing that their child will not likely have Tay-Sachs. However this may not be a realistic option if Faye and Michael are determined to raise a child "of their own flesh and blood."
- Can you think of any other alternatives available to Faye and Michael?

Of the options we’ve listed, is one more or less acceptable than the others? To what extent is Faye and Michael's decision theirs alone? Are there social norms or values that would make any of the options more or less acceptable?

2. Should the public health care system ensure that genetic testing is available to any Canadian who wants it? Should the health system cover the cost? Should the system cover some tests, but not others? If some tests are not covered, to what extent should they be available to people who are willing to pay for them? Who should make these decisions, and on what basis?

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Scenario B. Prenatal Genetic Testing
Adapted from a Scenario Composed by Ted Schrecker

Instead of dealing with a specific condition, this scenario refers to Condition X, to highlight the element of the genetic testing debate that has to do with the nature of the conditions to be detected.

Susan and her husband Jean-Claude know that there is a history of Condition X in both of their families. When Susan finds out she is pregnant, she asks her doctor whether there is a test that can determine whether the fetus:

- will be affected by the disorder; or
- will be a carrier of the disorder who can pass it on to future generations.

The test is available, so Susan and Jean-Claude decide to have it performed as early as possible in the pregnancy. Prior to having the test performed, Susan and Jean-Claude hear a radio interview with a medical geneticist, who says it would be truly unfortunate for a child to be born with Condition X when genetic testing can diagnose the disorder prenatally.

Discussion Questions -- Prenatal Genetic Testing

1. Let's say Condition X is Huntington's disease, and tests show that the fetus
will develop the disease. Huntington's symptoms do not appear until a person reaches middle age, so that he or she could make constructive, informed life decisions with the information available through genetic testing. On the other hand, advance knowledge of what the future holds could be devastating for the person and his or her family, even before the disorder develops. Should Susan terminate the pregnancy, or carry it to term?

2. What if Condition X is familial hypercholesterolemia, a condition that increases the likelihood of dying of heart disease by middle age, but can be treated through diet and other choices?

3. What if Condition X is WAGR syndrome, a rare hereditary disorder that can involve mental retardation, several kinds of cancer, and genito-urinary abnormalities?

4. What if people with Condition X could live almost as long as anyone else, but only if they had access to full-time care, either at home or in an institution? If Susan and Jean-Claude continue the pregnancy, who should pay for that care?

5. Susan and Jean-Claude did not plan their pregnancy and therefore did not seek counselling to discuss their options before Susan became pregnant. What form of counselling would be appropriate now? Who should provide the counselling? How can individual choices be respected?

6. Are there genetic tests that should or should not be funded by the public health care system? Who should decide which tests are funded? What criteria should be used to determine which tests are funded? If some tests are not covered, should they be available to people who are willing to pay for them, and to what extent?

7. Do you agree with the view expressed in the radio interview with the medical geneticist? Does your answer depend on what Condition X is? How could the geneticist's point of view affect people who are already living with Condition X, and their families? How could our answers affect social attitudes, and even legal attitudes, toward people with genetic disorders?

8. Many genetic tests are now being developed and marketed by private companies. What should these companies, and industry as a whole, be doing to inform consumers and health professionals about the possibilities and limitations of genetic testing?

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Scenario C. Selecting for Genetic Traits
(Adapted from GenEthics Consortium Case Literature NHGRI at NIH)²

Harry and Martha are worried about having a second child with Severe Combined Immune Deficiency (SCID). Children born with SCID have seriously impaired immune systems, as a result patients may succumb to any number of infections. As recently as 20 years ago, children with SCID died early in life, but the use of bone
marrow transplants has greatly extended survival and, in some cases, led to better quality of life. In general, results are best when a transplant is done early, and when the marrow donor and recipient have similar genes that code for Human Leukocyte Antigens (HLAs). HLAs are a family of cell surface proteins that are critical for the activation of immune responses. The HLA genes are the most variable set of human genes known and a close match is most likely if the donor is a brother or sister.

Harry and Martha have signed up with a new private clinic that offers pre-implantation genetic diagnosis (PGD). With this technique, a number of the woman’s eggs are fertilized by her partner’s sperm in a laboratory, and each of the embryos is tested before being reimplemented in her womb. This makes it possible to select embryos that are free of genetic disease.

Harry and Martha tell the medical geneticist they want to undergo PGD so they can begin their pregnancy knowing that the baby won’t have the disorder. A few weeks later, they give a second reason: Their six-year-old daughter with SCID is getting sicker with the disease, and they hope to use bone marrow from a second child to save their daughter. Is it possible, they ask, to test the healthy embryos for HLA genetic compatibility and transfer only those that most closely match their daughter’s type?

The geneticist knows that the technology can be used in this way, but wonders whether agreeing to the couple’s request would be ethical.

Discussion Questions

Genetic Traits vs. Genetic Disorders

1. PGD can be used to identify embryos that are less likely to develop specific disorders, like muscular dystrophy or Down Syndrome. Harry and Martha asked the geneticist to select embryos that were free of the SCID mutation and had genes that were compatible with their daughter’s. But a person’s HLA status is not a disorder it’s a genetic trait, just like his or her gender, or the colour of his or her eyes or hair.

   a. Is it ever appropriate to select an embryo based on genetic traits, rather than disorders?
   b. Should the decision be up to the individuals involved?
   c. Are there social norms or values that make it acceptable or unacceptable to select embryos for their genetic traits in certain situations?

Fate of the Unselected Embryos

2. The PGD procedure involves fertilizing a number of eggs in a laboratory (in vitro fertilization). In Harry and Martha’s case, if the geneticist agreed to their request, only those embryos that were free of the SCID mutation and compatible with their daughter’s HLA genes would be implanted.

   a. What should be done with the embryos that have been screened out?
   b. Should the couple donate them for medical research?...store them for later use?...donate them to other couples for in vitro fertilization?...or have them destroyed?
   c. Is the couple’s decision completely up to them, or are there social norms or values that would argue for or against any of these options?
PRIVACY AND CONFIDENTIALITY ISSUES
OF TEST RESULTS

1. State laws now exist requiring confidentiality of genetic testing.

2. Privacy = Control over access to others!
   Confidentiality = Control after access given to someone

3. Generally - a person controls or "owns" whether his/her DNA given for testing (not property right once given however - Moore vs. Regents UC!!) or if given for testing whether results are disclosed.

4. Legal Issues

a. Relative's duty to provide DNA for linkage studies - It could benefit from treatment or serious illness if deadly information minimal (e.g., cheek swab), state could override privacy interests vs. routine DNA sample to be given!!

b. Physician's duty to inform at risk relatives - e.g., cancer - health protection overrides privacy issue! Must inform relatives if prevent harm to others!

Tatevatt vs. Regents UC - a psychiatrist must inform - person who is at risk as a result of information obtained from patient!
State Genetic Privacy Laws

Last updated: 4/15/02

Medical information is presumed confidential, but increasing capabilities to store and rapidly transfer data escalate the challenge of protecting privacy. Laws in all states restrict access to medical records. At issue is whether genetic information should be protected generally, as another component of health data, or by special genetic privacy laws.

The case against "genetic exceptionalism" asserts that genetic information is fundamentally no different than other health data and special protections for one type of information could deny safeguards that should be established more generally. Proponents argue that the stability of genetic information and unique predictive - rather than merely historic - qualities warrant special consideration.

Laws in 16 states require informed consent for a third party either perform or require a genetic test or to obtain genetic information. Twenty-three states require informed consent to disclose genetic information. In addition, Rhode Island and Washington require written authorization to disclose genetic information. Colorado, Florida, Georgia, and Louisiana explicitly define genetic information as personal property. In 2001 Oregon repealed its property right to DNA samples and genetic information. Four states mandate individual access to personal genetic information, and 17 states have established specific penalties - civil or criminal - for violating genetic privacy laws.

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<th>State and Statute</th>
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<th>Define as Personal Property</th>
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<td>California</td>
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1 Limits disclosure of and access to genetic information by employers and insurers.
2 Requires written authorization only
1. Several States now have laws preventing genetic testing & discrimination in the workplace. Including CA.

2. Many states prohibit discrimination on the basis of specific genetic traits—e.g., sickle-cell.

3. U.S. American Employment law is based on "at will" rule—employers free to hire or fire people for no reason unless protected by collective bargaining agreements—now protect against race, gender, handicap, genetic discrimination, etc.

4. State laws vary from state to state.
1. **ADA** - Americans with Disability Act (1990) enforced by Equal Employment Opportunity Commission (EEOC). EEOC in 1995 interpreted the ADA to include genetic predisposition/diseases - not including carriers!

2. **Title VII of 1964 Civil Rights Act** - prohibits discrimination on basis of race, sex, religion, or national origin. Could include genes if present at high level in a particular group (e.g., sickle cell).

3. **OSHA** - Occupational Safety & Health Act

   Employers required to furnish employees a place of employment free of hazards!

   What if employee has genetic condition making him/her sensitive to workplace environment? Could require testing — Carpal tunnel syndrome case —

4. **Clinton Executive Order - 2000**

   Prevents/Prohibits Federal Employees from being discriminated against on basis of genetics/gene
State Genetics Employment Laws

Several states acted against employer use of genetic information in the 1970s and '80s to prohibit employer discrimination against applicants with the sickle cell trait. Wisconsin was the first state to ban genetic testing and discrimination in the workplace in 1991. With Hawaii, Utah and Virginia enacting measures in 2002, genetic nondiscrimination in employment laws are in place in 31 states. The scope and functions of these laws vary widely. All laws prohibit discrimination based on the results of genetic tests; many extend the protections to inherited characteristics, and some include test result of family members, family history and information about genetic testing, such as the receipt of genetic services. Most states also restrict employer access to genetic information, with some prohibiting employers from requesting, requiring and obtaining genetic information or genetic test results, or directly or indirectly performing or administering genetic tests.

On the federal level, the Equal Employment Opportunity Commission in 1995 interpreted “disability” in the Americans with Disabilities Act to include genetic predisposition to disease, but conflicting rulings raise questions whether the Supreme Court would accept the EEOC interpretation. President Clinton in February 2000 banned genetic discrimination in the federal workplace and called on Congress to pass a federal genetic information nondiscrimination law for private sector employment.

The U.S. Senate debated the matter during the summer of 2000, but took no action.

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<tr>
<th>State and Statute</th>
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The dark side of genetic testing
Railroad workers allege secret sampling

By Dana Hawkins

John Wiebelhaus, a fourth-generation railroad man, makes his living with his hands, laying miles of track, repairing heavy steel rails, and picking ice from the track's switches. Tough work—but Wiebelhaus loves it. "I like the idea that tracks I lay could be there 100 years," he says. "It's in my blood."

That may not be all that's in his blood, which is why the track-maintenance foreman claims, his employer, the Burlington Northern Santa Fe Railroad, has been secretly testing the blood of workers with carpal tunnel syndrome. "The railroad wants to be able to say: 'You were a time bomb. Because you are genetically predisposed to the disease, you would've gotten it whether you were a soda jerk or running a jackhammer,'" says Harry Zanville, an attorney for the railroad's union that last week filed a lawsuit, along with Wiebelhaus, to force the company to stop the alleged covert testing. He claims that 125 workers recently gave blood samples and that at least 18 were subjected to gene tests without the employees' consent. The reason: Money, says Zanville, insisting the company hopes to avoid paying out millions in medical bills and disability to workers who develop the painful musculoskeletal disorder on the job.

The federal court lawsuit, the first of its kind against a private company, charges that the furtive testing violates the Americans with Disabilities Act and several state laws barring DNA testing by employers. The U.S. Equal Employment Opportunity Commission filed a separate petition, also in a federal court in the Northern District of Iowa. The EEOC alleges that the Fort Worth-based railroad required blood samples from workers who had submitted claims arising from carpal tunnel injuries. The blood was then allegedly tested for a genetic defect that may predispose a person to some forms of the ailment. Athena Diagnostics, the lab that allegedly conducted the tests, is also a defendant in the union's case.

Hidden reason. Gary Avary, a BNSF employee, says he discovered the alleged covert sampling last month after he received a letter from his employer directing him to get his blood tested. The Nebraska track laborer had recently returned to his job after successful carpal tunnel surgery. The lawsuit alleges that when his wife, a registered nurse, inquired about the test "the secret intentions of the BNSF were inadvertently revealed." After Avary refused to take the test, the company informed him that he would be investigated for failing to cooperate. A railroad spokesperson says BNSF doesn't require workers to submit to genetic testing but that "some employees were asked to take a test."

The railroad employees are encouraged by a federal court's approval last December of a settlement in a case involving the genetic privacy rights of workers at Lawrence Berkeley Laboratory. As first reported by U.S. News, LBL workers for decades were tested without their knowledge for syphilis, pregnancy, and the genetic trait for sickle cell disease. President Clinton last year banned genetic discrimination against federal employees, but Congress has not extended the rule to the private sector. "It's important for the public to have confidence that genetic tests will be used for their benefit," says Paul Billings, codirector of GeneSage, a company that promotes responsible DNA screening. "Unfortunately, this case suggests that we're still in the dark ages of employment-based testing."

Geneticists in particular question the legitimacy of the carpal tunnel test. They point out that there are no genes for common workplace disability, and that the mutations are extremely rare. "It's a humanitarian physician. I try hard to make the world a better place," says Philip Chance, a geneticist at the University of Washington in Seattle, who discovered one of the mutations. "This would be the last thing I'd want to see happen with my work."

What is Carpal Tunnel Syndrome?
Carpal tunnel syndrome occurs when tendons or ligaments in the wrist become enlarged, often from inflammation, after being aggravated. The narrowed tunnel of bones and ligaments in the wrist pinch the nerves that reach the fingers and the muscles at the base of the thumb. The first symptoms usually appear at night. Symptoms range from a burning, tingling numbness in the fingers, especially the thumb and the index and middle fingers, to difficulty gripping or making a fist, to dropping things. Some cases of carpal tunnel syndrome are due to work-related cumulative trauma of the wrist. Diseases or conditions that predispose to the development of carpal tunnel syndrome include pregnancy, diabetes, and obesity.

Is there any treatment?
Carpal tunnel syndrome is treated by immobilizing the wrist in a splint to minimize or prevent pressure on the nerves. If that fails, patients are sometimes given anti-inflammatory drugs or injections of cortisone in the wrist to reduce the swelling. There is also a surgical procedure in which doctors can open the wrist and cut the ligament at the bottom of the wrist to relieve the pressure. However, only a small percentage of patients require surgery.