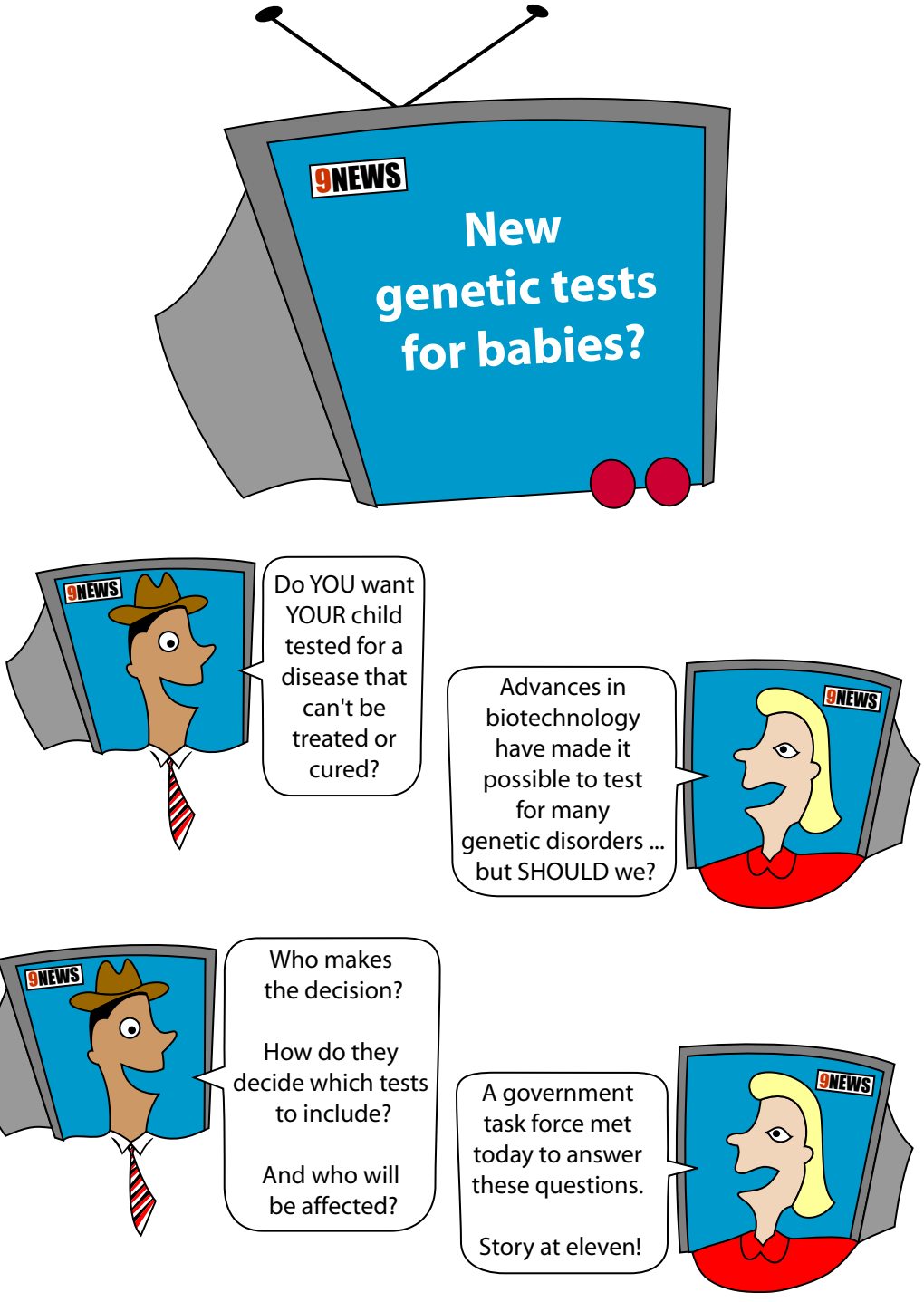
Genetic Screening of Newborn Infants: What Should We Test And Why?

Activity Resources Packet



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1. YOUR CHALLENGE

Dear _____,

With a prick of the heel we now have the ability to screen newborns for many genetic disorders. Information gleaned from The Human Genome Project and ever-improving technologies have identified numerous genes that may carry mutations causing genetic disorders. Simple tests for many of these disorders have been developed and more promise to follow. As we consider the wide-scale use of these tests to screen for disorders in newborns, the need to create and adopt a public policy to guide actions and decisions about these tests has become clear.

I am asking you to serve as a member of a Task Force to create a public policy on newborn genetic screening. In developing your policy, I am asking the Task Force to first study and then consider:

- The specific disorders
- The choice of tests available
- The technology involved
- The cost of the tests
- The rights of the child and parents
- The personal and societal impacts of wide-scale screening

In order to facilitate your group's work, I have gathered all of the necessary information and provided a more detailed list of issues to consider. Your policy will be written and/or presented, should address issues other than specific tests to be given (see above key points), and be realistic and appropriate for your area.

I look forward to examining the policy your group creates.

Sincerely,

Your Government Official

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2. WHAT IS A TASK FORCE?

A Task Force is a group of concerned and informed people. They are selected to study all sides of an issue, consider their own view and that of the group, and recommend how the government should deal with the issue in question. For a balanced committee, you will need five to six "stakeholders," who are people with particular expertise and interests. Stakeholders on your Task Force might include a doctor, lawyer, legislator, concerned parent, lobbyist or health insurance representative. Brief descriptions of these roles are outlined below. Other members with different roles can also be included, such as a genetic counselor or representative of the religious community. Staff your Task Force with stakeholders who you think are most important in discussing this issue.

You Become a Stakeholder - Select A Role To Play

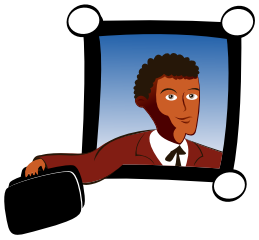
Doctor:

You are a specialist in genetic disorders, concerned about childrens' health and well-being. You believe that genetic testing will assist doctors in providing better medical care. Not only do you know a lot about genetic disorders, you also realize how important it is to teach the public and the parents of newborns about these disorders.

Some of your questions are:

- What treatments are available for each disorder, and at what age does treatment begin?
- How sensitive and reliable is each test?
- How should health care workers counsel parents and families?
- What laws are needed to protect doctors?

Lawyer:



You are concerned about protecting the rights of the individual and the rights of health care institutions. You know many legal issues will arise with an expanded screening program.

Some of your questions are:

- Who keeps the screening results? Who has access to them? What are the confidentiality issues?
- Will hospital administrators be sued over testing errors or if tests are not given?
- Should parents have the right to refuse screening?
- Are laws needed to protect citizens' or doctors' rights?

Legislator:

Your major concern is that any screening program must be cost-effective. But you also see the importance of a comprehensive screening program for public health and disease prevention. With a limited budget, you know that an expanded genetic screening program for newborns could sacrifice some other health program. As an elected official, you also pay attention to public opinion.

Some of your questions are:

- How much will the proposed genetic screening program cost and who will pay for it?
- Based on demographics, how many people in my constituency are likely to be affected by each genetic disorder?

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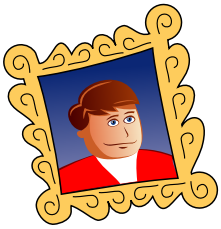
- How will constituents who do not have children react to their tax money being used for newborn screening as opposed to something else that would benefit them personally?
- What policies have other governments enacted?

Lobbyist for a genetic disorder interest group:

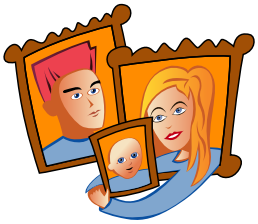


You speak for those affected by genetic disorders. The efforts of your forerunners led to the initiation of newborn genetic screening in the 1960's. You support genetic screening when early identification and treatment of a disorder will make a difference to that person.

Some of your questions are:

- Are the proposed tests the most sensitive and reliable ones available?
- Who will have access to the screening results?
- Will test information result in prejudice against individuals with genetic disorders?
- Will test information make it difficult for an individual to obtain health insurance? Will a predisposition to a genetic disorder be considered a "pre-existing condition"?

Parent of a newborn infant:



You are concerned about the health of your newborn, both now and as the child grows up. Your child was screened for several genetic disorders soon after birth. You have heard that tests for other genetic disorders are available and wonder if your child should have been screened for those as well. Your concerns extend to the parents of other newborns as well.

Some of your questions are:

- What are the effects of the genetic disorders to be tested, and how can they be treated?
- What genetic tests are available?
- Will parents be able to choose or refuse tests?
- Will testing (or lack of testing) be a source of distress for newborns or their parents?

Parent of a child with a genetic disorder:

Your 1-year-old child was not tested for this disorder at birth, but only later after symptoms appeared. You wonder if newborn screening would have led to earlier and perhaps more effective treatment for your child. You oppose providing genetic screening only to those who can be identified as belonging to particular racial and ethnic groups, since some infants who have the disorder but who do not belong to those groups may be missed. You voice the concerns of other parents whose children have genetic disorders.

Some of your questions are:

- What are the effects of each genetic disorder to be tested, and how can it be treated?
- What tests are available, and how sensitive and reliable are they?
- Who will have access to the test results?
- Will test information result in prejudice against individuals with genetic disorders?

Officer from a health insurance company:

You know that genetic screening will add to the cost of health care. However, you also know that early identification of some genetic disorders can lead to improved treatment and decreased health care cost in the long term. You would like access to test results to help predict insurance costs.

Some of your questions are:

- What is the cost per test and the total for screening?
- Who will pay for the screening program?
- Are the benefits of an expanded testing program worth the cost?
- Will early identification of persons with genetic disorders lead to cost savings in treatment or care?

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3. KEY ISSUES

Here are some issues that your Task Force might consider. As a committee, select those issues that seem most important or for which you have information. You may also identify other issues that you want to consider.

1. Choice of tests

- What are the effects of each genetic disorder considered by the Task Force?
- What treatment is currently available for each genetic disorder, and at what age does treatment begin?
- Are tests currently available for each genetic disorder? If so, what are they?
- Should tests be restricted only to those disorders that are treatable? Only those for which treatment early in life makes a difference? Why?
- Based on demographics, how many people are likely to be affected by each genetic disorder?
- How do demographics influence the choice of tests?
- Should all newborn infants receive the same screening tests? Why or why not?

2. Technology

- How sensitive and reliable is each test?
- Can a test in question be performed on a large scale in laboratories? Why or why not?

3. Costs

- What is the cost per test and the total for screening?
- Will early identification of persons with the genetic disorder lead to cost savings in treatment or care? Why or why not?
- Who will pay for testing?
- Should citizens who do not have children help pay for newborn testing? Why or why not?

4. Rights

- Is testing fair to a newborn child who cannot speak for his or her own rights? Why or why not?
- Should parents be able to choose or refuse tests? Why or why not?
- If the symptoms of a genetic disorder are not expected to appear until after a child reaches legal adulthood, should that disorder be included in a newborn testing program? What are the pros and cons?
- Who has access to the test results?
- What happens to the blood samples after testing?
- Are laws needed to protect citizens' or doctors' rights? If so, what types of laws?

5. Personal and societal impacts

- Will test information result in prejudice against certain individuals? If so, why? How might this be expressed?
- Will testing (or lack of testing) be a source of distress for parents or newborns? If so, why?
- Will test information make it difficult for an individual to obtain health insurance? Will a predisposition to a genetic disorder be considered a "pre-existing condition"?
- How will early diagnosis of genetic disorders help or hurt society?
- What are current policies in different states or countries?

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4. WHAT IS NEWBORN GENETIC SCREENING?

The history of newborn screening

Newborn genetic screening is a health program aimed at identifying infants who have genetic conditions that can be helped by early intervention. In many cases, this early intervention means the elimination or reduction of symptoms that would have left an unscreened individual with a lifetime of disability. Newborn screening is more than just testing.

The genetic screening system in its most ideal form involves:

- The initial screening test
- Short-term follow-up
- Diagnosis
- Treatment and management
- Evaluation

Genetic screening began in the 1960s with the development of the Guthrie test for phenylketonuria (PKU). PKU is easily treated by restricting certain foods from the diet, but if left untreated, the disorder causes severe mental retardation.

The initial push for mandatory PKU testing came from the test's developers and public interest groups, such as associations for mental retardation. In 1962, Massachusetts launched a voluntary newborn screening program for PKU, demonstrating that mass screening for a genetic disorder was indeed feasible. However, health care providers in other regions were slow to implement newborn screening for PKU because it was not clear who was actually responsible for conducting the test - the hospital where the infant was born, the mother's obstetrician or a pediatrician.

Public and industry pressure to test for PKU continued and states began to adopt screening programs before the disorder, its test and/or its treatment were completely understood. At that time, the state health departments and legislature played no part in regulating newborn screening programs. Some organizations raised concerns about the accuracy of test results, how best to conduct early treatment, and quality control. These issues became even more pronounced as tests for other genetic disorders were added to screening programs. Federal funding for PKU screening was made available in 1976, along with laws mandating the testing. Today, newborn genetic screening programs have been initiated in all developed countries worldwide. Policy-makers in these countries carefully consider the best interests of everyone involved before adopting a new test. Several different organizations, including the World Health Organization, the Institute of Medicine and the Council of Europe have established guidelines to help develop policy on screening programs, but this remains a difficult and controversial issue.

Currently, all guidelines determine clinical value based on:

- **Incidence:** The disorder must affect enough individuals to make screening worthwhile.
- **Clear benefits:** Infants should both benefit and be protected by newborn screening systems. The benefits of the test must outweigh any negative consequences.
- **Treatment:** An effective treatment for the disorder must be available for all newborns screened. Early treatment should be more beneficial than treatment later in life.
- **Cost:** Screening should avert costs that would have been incurred if the disorder had not been identified.
- **Feasibility:** It must be possible to run the test in large numbers with high accuracy.

Using pilot studies

When genes involved in disorders are newly identified, tests for those disorders can be considered for inclusion in screening programs. However, not all genetic conditions are good candidates for screening. In order to avoid problems like those encountered in initiation of PKU screening, many programs use a pilot study to help them make informed decisions about inclusion of new tests. For example, the Quebec newborn screening program conducted a pilot study of the test for galactosemia and determined that this test was inefficient in their population. Also, several U.S. states and countries are currently conducting pilot studies of cystic fibrosis testing. Often, uncertainties about whether a test should be included can be addressed by a pilot study. In this "test of the test," clinical value can be determined by studying a sample population that represents the target population.

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Why do we need newborn screening policies?

New developments in genetic technologies raise ethical, legal and social issues requiring policy decisions. Genetic screening programs must be reevaluated frequently as new disorder associated genes are identified, new testing methods are developed, and treatments for genetic disorders continue to improve. Controversial issues such as storage of genetic information, the right to refuse testing, genetic discrimination and deciding which disorders to include in screening programs are currently being evaluated by policy-making committees.

Who decides newborn screening policy?

In the United States, the federal government has no constitutional right to require genetic screening, so most genetic screening policy and legal matters are left up to individual states. Similarly, in Europe, each country develops its own policy and legislation. Newborn screening systems vary according to public health infrastructure, laboratory capacity, screening techniques used, community values, demographics and financing mechanisms. These variables lead to differing policies.

What tests are included in screening programs?

The disorders included in newborn screening programs vary a great deal from state to state and from country to country. All U.S. states screen for PKU and hypothyroidism, but only some screen for sickle cell disease, galactosemia, maple syrup urine disease or cystic fibrosis. All western European countries, except Finland, screen for PKU but vary in screening for other disorders. Thus, while an infant may belong to an ethnic group at high risk for a particular genetic disorder, he or she will be denied the important benefit of screening for that disorder if born in certain states or countries.

Table 1 lists some of the tests required for newborns in the United States and around the world. This sample illustrates the similarities and differences between states and countries in required newborn genetic testing. Only six genetic disorders are included in the table; many areas screen newborns for additional disorders.

What tests are not included in screening programs?

The disorders listed below are not currently tested for in any screening program. However, tests have been developed for them and they could be considered for inclusion in newborn screening programs:

- Alpha-1-antitrypsin deficiency
- Alzheimer's disorder
- Breast cancer susceptibility
- Huntington's disease
- Neurofibromatosis 1
- Smith-Lemli-Opitz syndrome

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Table 1: Disorders tested for in newborn screening programs in the United States (as of 6/27/03) and other countries

Region	PKU	Hypo-thyroidism	Galacto-semia	Sickle cell disease	Maple syrup urine disease	Cystic fibrosis
United States						
Alabama	√	√	√	√	x	x
Alaska	√	√	√	√*	√	x
Arizona	√	√	√	√	√	x
Arkansas	√	√	√	√	x	x
California	√	√	√	√	√*	x
Colorado	√	√	√	√	x	√
Connecticut	√	√	√	√	√	√*
Delaware	√	√	√	√	√	x
District of Columbia	√	√	√	√	√	x
Florida	√	√	√	√	x	x
Georgia	√	√	√	√	√	x
Guam	√	√	√	√	√	√
Hawaii	√	√	√	√	√	x
Idaho	√	√	√	x	√	x
Illinois	√	√	√	√	√	x
Indiana	√	√	√	√	√	x
Iowa	√	√	√	√	√^	x
Kansas	√	√	√	√	x	x
Kentucky	√	√	√	√	x	x
Louisiana	√	√	√	√	x	x
Maine	√	√	√	√*	√	x
Maryland	√	√	√	√	√	x
Massachusetts	√	√	√	√	√	√^
Michigan	√	√	√	√	√	x
Minnesota	√	√	√	√	√	x
Mississippi	√	√	√	√	√	√
Missouri	√	√	√	√	x	x
Montana	√	√	√	√*	x	√^
Nebraska	√	√	√	√	√*	x

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Table 1 *continued*

Region	PKU	Hypo-thyroidism	Galacto-semia	Sickle cell disease	Maple syrup urine disease	Cystic fibrosis
Nevada	√	√	√	√	√	x
New Hampshire	√	√	√	√*	√	x
New Jersey	√	√	√	√	√	√
New Mexico	√	√	√	√	x	x
New York	√	√	√	√	√	√
North Carolina	√	√	√	√	√	x
North Dakota	√	√	√	√	√	x
Ohio	√	√	√	√	√	x
Oklahoma	√	√	√	√	x	x
Oregon	√	√	√	√	√	x
Puerto Rico	√	√	√*	√	x	x
Pennsylvania	√	√	√	√	√	√
Rhode Island	√	√	√	√	√	x
South Carolina	√	√	√	√	x	x
South Dakota	√	√	√	√*	√*	x
Tennessee	√	√	√	√	x	x
Texas	√	√	√	√	x	x
Utah	√	√	√	√	x	x
Vermont	√	√	√	√	√	x
Virgin Islands	√	√	√	√	√	x
Virginia	√	√	√	√	√	x
Washington	√	√	x	√	x	x
West Virginia	√	√	√	√*	x	x
Wisconsin	√	√	√	√	√	√
Wyoming	√	√	√	√	x	√
Canada						
Alberta	√	√	x	x	x	x
British Columbia	√	√	√	x	x	x
Manitoba	√	√	√	x	x	x
New Brunswick	√	√	x	x	x	x
Ontario	√	√	x	x	x	x

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Table 1 *continued*

Region	PKU	Hypo-thyroidism	Galacto-semia	Sickle cell disease	Maple syrup urine disease	Cystic fibrosis
Quebec	√	√	x	x	√	x
Other countries						
Argentina[1]	x	x	x	x	x	x
Austria	√	√	√	x	x	√
Australia	√	√	√[3]	x	x	√[4]
Belgium	√	√	x	x	x	x
Brazil (most states)	√	√	x	√	x	x
Cyprus	√	√	x	√	x	√*
Czech Republic	√	√	x	x	x	√*
Denmark	√	√	x	x	x	x
Finland[2]	x	√	x	x	x	√*
France	√	√	x	√*	x	√ ^
Germany	√	√	√	x	x	x
Greece	√	√	x	√	x	√ ^
Hungary	√	√	√	x	x	√
Ireland	√	√	√	x	√	√
Israel	√	√	x	√*	x	x
Italy	√	√	√	x	x	√*
Japan	√	√	√	x	√	√
The Netherlands	√	√	x	x	x	x
New Zealand	√	√	√	x	√	√
The Philippines	√	√	√	x	x	√
Slovakia	√	√	x	x	x	x
Switzerland	√	√	√	x	x	x
United Kingdom (England, Scotland, Wales, Northern Ireland)	√	√	√	√*	x	√*

* Indicates test is not required (selected populations, limited pilot or by request)
^ Indicates this is a pilot testing program.
[1] Argentina currently has no newborn screening program.
[2] PKU does not exist in Finland and cystic fibrosis is rare.
[3] except Victoria
[4] except Western Australia

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5. GENETIC DISORDER INFORMATION SHEETS

Short Medical Summary of Disorders

Disorder	Incidence (Approximate)	Symptoms if Not Treated	Treatment
Alpha-1-antitrypsin	1 in 2,000	Early lung disorder (by 40 years old).	Life style choice and environmental precautions (for example, no smoking, clean workplace); Prolastin injections.
Alzheimer's disorder (associated with APOE e4 allele)	1-3 percent of the population is homozygous for APOE e4. 30-50 percent of these people will develop Alzheimer's.	Increasing dementia. Progressive loss of mental ability and changes in personality.	Alzheimer's disorder can be managed but not cured.
Breast cancer	1 in 8 women will develop breast cancer. Only 5-10 percent of cases have a genetic link; two thirds of those are associated with mutations in BRCA1 or BRCA2 genes.	Increased risk for breast cancer.	Improved diet and exercise. Early screening. Surgical removal of all or part of a breast before tumor onset.
Cystic fibrosis	1 in 2,000 Caucasians 1 in 17,000 African-Americans 1 in 9,000 Hispanics	Obstructive lung disorder, frequent infections and heart failure, eventually resulting in death.	Physical therapy, antibiotics, oxygen therapy and organ transplants. Gene therapy is currently under trial.
Galactosemia	1 in 40,000	Severe brain and kidney damage; can cause death if untreated.	Galactose-restricted diet.
Huntington's disease	1 in 20,000 in Western countries, less frequent in Africa and Asia	Gradual deterioration of the nervous system.	None. However, genetic screening allows the individual to plan for their future and decide whether to have children.
Hypo-thyroidism	1 in 4,000	Mental retardation, other brain damage and growth delay.	Provide thyroid hormone.
Maple syrup urine disease	1 in 90,000 to 1 in 300,000 1 in 176 in Pennsylvania Mennonites	Vomiting, seizures, severe mental retardation, coma. Death in 2 years	Lifelong strict dietary regimen and monitoring of amino acid levels.
Neuro-fibromatosis 1	1 in 4,000	Skin tumors, vision problems, learning difficulties, and skeletal abnormalities.	Monitoring of tumors. Treatment of rare cancers. Treatment of skeletal abnormalities through surgery. Intervention for learning disabilities.
Sickle cell disease	1 in 400 African Americans 1 in 58,000 Caucasians 1 in 1,100 in Hispanics from eastern United States 1 in 32,000 in Hispanics from western United States 1 in 11,500 Asians 1 in 2,700 Native Americans	Acute pain from blocked blood vessels, tissue and organ damage, increased risk of infection, and associated complications.	Early comprehensive care and penicillin treatment reduces illness and death.
Smith-Lemli-Opitz syndrome	1 in 10,000 to 1 in 50,000	General growth retardation, developmental delay, and a variety of different malformations.	Supplying missing cholesterol early in life can eliminate a large portion of the disorder symptoms.

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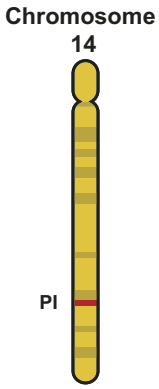
Alpha-1-antitrypsin Deficiency

Clinical description

Alpha-1-antitrypsin deficiency can lead to early onset of emphysema (a degenerative lung disorder) and/or liver failure. These symptoms usually appear when a person is in their 30's or 40's. Symptoms are more severe in smokers than in nonsmokers.

Genetics



This disorder is caused by a mutation in the proteinase inhibitor (PI) gene on chromosome 14. The normal protein coded for by this gene is involved in tissue repair. Disorder symptoms depend on which type of mutation an individual has in the PI gene. There are more than 70 different alleles of the PI gene. The M allele is the most common non-disease causing (normal) variant. The mutant alleles S and Z are the most common disease-causing variants. Individuals homozygous for the Z allele (PI ZZ) are at high risk for emphysema and liver disease. Individuals homozygous for the S allele (PI SS) do not display symptoms of the disease. However, individuals with one copy of the Z allele and one copy of the S allele (PI SZ) may develop emphysema.

Inheritance

Autosomal recessive.

Incidence

The incidence of the disorder in the United States is approximately 1 in 2,000. Only 10 - 20 percent of these individuals will develop liver disease. PI ZZ and PI SS are found in 1 in 2,500 Caucasians in the United States. Because the heterozygote genotype occurs in relatively high frequency (1 in 10 people of European origin are either MZ or MS), the PI SZ genotype is also relatively frequent.

Diagnosis without genetic screening

Diagnosis is only made at the onset of emphysema or other symptoms of the disorder.

Clinical outcome without screening and treatment

Early onset emphysema and/or liver failure are expected.

Clinical outcome with screening and treatment

Early identification can enable individuals to receive the education needed to allow them to effectively evaluate career options, lifestyle choices and insurance needs. In some situations, onset of emphysema, liver failure and other symptoms can be delayed by altering life style. For example, parents of affected individuals can choose not to smoke near the affected child. As an adult, the affected individual can choose not to smoke and to work in a smoke-free environment.

There has been great success in using weekly injections of a drug called Prolastin to restore alpha-1-antitrypsin levels to normal in patients with the PI ZZ genotype. This drug can delay or prevent onset of symptoms. However, it is generally given to patients at the first onset of symptoms, such as mild emphysema, because many people do not know they have alpha-1-antitrypsin deficiency until symptoms appear. The safety and effectiveness of this treatment for children has not yet been determined.

Prolastin costs about $25,000 U.S. per year per patient and is not available in the UK. This cost is so high because Prolastin is derived from human blood plasma which fluctuates in supply and because only one company, Bayer, manufactures it.

The price of Prolastin and its limited availability has caused a great deal of controversy. In January 2000 a home health care company, anticipating a shortage in supply of the drug, stockpiled Prolastin and raised the price even more for patients. PPL Therapeutics (famous for their cloned sheep, Dolly) has now developed a technique for producing the drug using transgenic sheep. They have inserted a gene for alpha-1-antitrypsin into the sheep, who excrete the gene product in their milk, from which it can be separated and purified. They have formed a partnership with Bayer and are currently conducting clinical trials. Since it does not rely on the supply of human blood

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plasma, this technique may significantly reduce the cost of treatment.
Other treatment options are limited. However, gene therapies are currently in development and have shown preliminary success in mice.

Testing

This disorder can be detected by testing the levels of alpha-1-antitrypsin in blood. If they are abnormally low, the next step is to identify the exact alpha-1-antitrypsin protein variants the person carries. Abnormal forms of the alpha-1-antitrypsin protein can be detected using dried blood as a sample for gel electrophoresis.

Genetic counseling

The association between alpha-1-antitrypsin and liver disease was not identified until 30 years ago, so many families are unaware that they may be transmitting alpha-1-antitrypsin deficiency. Genetic counseling can help families find out as much as they can about the disorder, its possible outcome and the effect it will have on their child's life. However, the effects of alpha-1-antitrypsin deficiency are not predictable. This presents a moral dilemma to families who know they carry the mutation and to health care professionals who may be in the position of counseling them.

References

The Alpha-1-antitrypsin Deficiency Association
http://www.alpha1.org/
Contains comprehensive, easy to understand information on the disorder. The association aims to implement public screening for alpha-1 and offers a screening guide and free testing kits. Last site update May 3, 2001. Accessed May 14, 2001.

Dr. Robert J. Huskey's website on Alpha-1-antitrypsin
http://www.people.virginia.edu/~rjh9u/antitryp.html
Contains detailed and advanced information. Taken from Principles of Medical Genetics, Eds. Gelehrter and Collins, 1990 (Williams & Wilkins) about the genetic nature of the disorder. Maintained by Dr. Robert Huskey at the University of Virginia. Last site update November 10, 1998. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

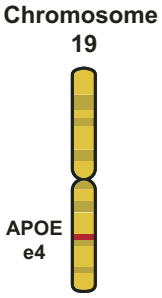
APOE e4 (associated with Alzheimer's Disease)

Clinical description

Alzheimer's disease is characterized by a progressive loss of function and death of nerve cells in several areas of the brain. This disorder is the fourth leading cause of death in the United States, affecting over four million Americans, most of them over the age of 70. Common symptoms include memory loss, disorientation, impaired judgment and personality changes.

Genetics

Many genes have been shown to be involved in the onset of Alzheimer's disease. One of these is Apolipoprotein E (APOE) located on chromosome 19. The APOE protein is responsible for moving fats between cells and absorbing cholesterol from foods in the intestine.



Inheritance

The APOE gene has three alleles: e2, e3 and e4. Since everyone inherits one allele of the APOE gene from each parent, there are six possible genotypes:

e2/e2
e3/e3
e4/e4
e2/e3
e2/e4
e3/e4

In Westernized populations, the e4 allele is associated with a risk for developing Alzheimer's disease. People with the e4/e4 genotype have the highest risk, but people with the e2/e4 or e3/e4 genotypes are also likely to develop the disease. While the APOE e4 allele defines a greater risk, the presence of e4 cannot alone predict the disorder prior to the onset of symptoms – only 40 percent of all Alzheimer's patients have the e4 allele. e4 is also associated with higher cholesterol absorption which leads to higher cholesterol levels in the blood.

Incidence

The most common APOE genotype is e3/e3, which occurs in 40 - 90 percent of people. The e2 allele is rare, occurring in only 2 percent of the population.

The e4/e4 genotype is found in only 1 - 3 percent of the Westernized population. However, the probability that a Westernized individual with the e4/e4 genotype will develop Alzheimer's disease is 60 percent, with women at greater risk than men. For individuals who consume high-cholesterol diets, having the e4 allele may also increase the risk of coronary artery disease.

The e4 allele is most prevalent in populations that still forage for food, such as Australian aborigines, sub-Saharan Africans and some Native Americans. However, it is not associated with Alzheimer's disease or coronary artery disease in these populations. Because foraging populations consume a low-cholesterol diet and need to absorb a higher amount of cholesterol, carrying the e4 allele may actually be advantageous.

Diagnosis without genetic screening

Standard clinical methods of diagnosing Alzheimer's disease combine physical and psychological testing. New diagnostic tools and criteria make it possible for physicians to make a positive clinical diagnosis of Alzheimer's with around 90 percent accuracy. Many criteria are involved in diagnosis including medical history, physical and neurological examination and psychiatric evaluation.

Clinical outcome without screening and treatment

Patients no longer function independently, and damage to the brain may result in seizures, coma, or death.

Clinical outcome with screening and treatment

Testing for and identifying the APOE e4 allele in patients may alter treatment options. Individuals with the APOE e4 allele respond less well to certain drug treatments than do individuals with other APOE alleles. Currently Alzheimer's disease can be managed, but not cured. Better management might be possible based on screening knowledge.

Genetic Screening of Newborn Infants: What Should We Test And Why?

Testing

Testing involves measuring levels of certain proteins in the patient and APOE genotyping.

Genetic counseling

The APOE e4 allele defines a risk for acquiring Alzheimer's disease but cannot predict the presence or absence of the disorder during an individual's lifetime.

References

The Alzheimer's Association
http://www.alz.org/
Contains information for people with the disorder and their families, physicians, researchers and the media. Provides an excellent help-line for specific questions about the disorder. Last site update April 13, 2001. Accessed May 14, 2001.

Alzheimer's Disease Education and Referral Center
http://www.alzheimers.org
Contains information services, research updates, multimedia educational materials, fact sheets, bibliographic database and clinical trials database. See their publications page *http://www.alzheimers.org/pubs/prog99.htm#Genetic Factors in AD Development* for specific information about the APOE e4 allele. Last site update May 14, 2001. Accessed May 14, 2001.

Corbo, R., Scacchi R. Apolipoprotein E (APOE) allele distribution in the world. Is APOE e4 a "thrifty" allele? *Ann. Hum. Genet.* 1999;63:301-310.
Discusses possible evolutionary reasons for the incidence of Alzheimer's Disease and ethic variability of allele prevalence. Advanced reading level.

St. George-Hyslop P. Piecing together Alzheimer's. *Scientific American* [serial online]. 2000. *http://www.sciam.com/2000/1200issue/1200Stgeorge.html*
Describes the physical changes that occur in the brains of Alzheimer's disease patients, genetic mutations that may lead to some of these changes and research into new treatments designed to counteract the effects of these mutations. High school reading level. Last site update December 2000. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

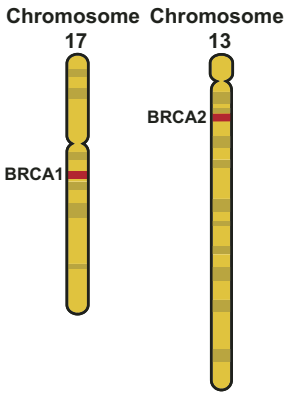
Breast Cancer Genes BRCA1 and BRCA2

Clinical description

Cancers cause cells in the body to change, to divide out of control (forming masses of tissue called tumors) and to spread to other parts of the body. They are named for the part of the body where they begin. Breast cancer, the second major cause of death by cancer in American women, is often detected when there are visible changes in the breast, such as a lump, thickening, swelling, skin irritation or nipple discharge. The risk of breast cancer increases with age.

Genetics

Only 5 - 10 percent of all breast cancer cases are believed to have a genetic link. Of these, an estimated two-thirds are caused by mutations in either BRCA1 or BRCA2, genes thought to play a role in fixing damaged DNA. About 50 - 60 percent of individuals with certain mutations in either of these two genes will develop breast cancer by age 70.



Inheritance

Autosomal dominant.

Incidence

The frequency of breast cancer in women is 1 in 8. Caucasian women have a higher risk of developing breast cancer than African-American, Asian or Hispanic women. The vast majority of affected women do not have a genetic predisposition to the disease. The prevalence of cancer-predisposing mutations in BRCA1 is 1 in 500 - 1000. The prevalence for BRCA2 mutations is unknown. A higher frequency of mutations in both genes is seen in the Ashkenazi Jewish population.

Diagnosis without genetic screening

Mutations in BRCA1 and BRCA2 are associated with early age of cancer onset, cancer in both breasts, and male breast cancer. Clinical breast exams and mammography can detect breast cancer at onset.

Clinical outcome without screening and treatment

Cancer can spread throughout the body if not treated and survival rate is reduced.

Clinical outcome with screening and treatment

There is no certain way to prevent breast cancer. However, some lifestyle risk factors have been identified including diet and alcohol use. It is important to identify breast cancer early to optimize treatment. If a genetic predisposition to breast cancer is known, there are drugs available which have been shown to reduce the likelihood of developing the disorder. Some high-risk women may consider a preventive mastectomy (removal of one or both breasts), although this does not guarantee that breast cancer will not develop. After such an operation, breast reconstruction may be possible and has become an important part of rehabilitation and therapy.

Testing

More than 235 mutations have been identified in BRCA1 and about 100 mutations have been identified in BRCA2. No currently available technique can detect all of the cancer-predisposing mutations in BRCA1 or BRCA2. Myriad Genetics has developed a test that analyzes about 16,500 base pairs for the two genes. The test costs $2,580 U.S. However, it is estimated that about 30 percent of BRCA mutations are not detected by currently available tests.

Genetic counseling

Genetic counseling for adults is offered before and after genetic testing. It is recommended that at-risk families consider a genetic testing strategy. Individuals with breast cancer in a family are strongly encouraged to be tested for mutations prior to unaffected family members. The test results from the affected family members will identify a particular type of mutation more likely to be associated with breast cancer. This information can then be used to test unaffected family members for the same mutation, thus making their results more meaningful.

Genetic Screening of Newborn Infants: What Should We Test And Why?

References

Breast Cancer Resource Center. American Cancer Society
http://www.cancer.org
Contains information on different breast conditions, prevention of breast cancer and genetic testing, with an emphasis on patient privacy and discrimination issues and treatment. Also useful fast facts, myths and self-exam information. Spanish language access available. Last site update May 14, 2001. Accessed May 14, 2001.

Kahn P. Coming to grips with genes and risk. *Science*. 1996;274:496-498. (in Research News).
This short review article addresses genetic testing for the breast cancer genes BRCA1 and BRCA2. It discusses the number of mutations in these genes, possible roles for the genes, the information that can and cannot be gained from genetic tests, the difficulties of translating test results into risk assessment, the interaction of environmental and genetic factors, and opposing viewpoints about the availability of commercial tests. An interesting figure shows the types of mutations (frameshift, non-sense, missense, etc.) found in each exon and intron of the two genes. High school reading level.

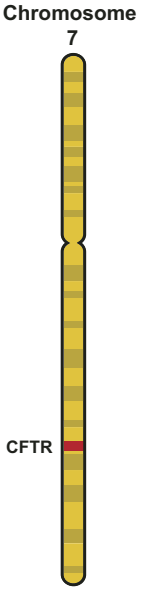
OncoLink: Breast Cancer
http://oncolink.upenn.edu/disease/breast/
Contains general cancer information, support groups, prevention, treatment, recommendations for screening, types of screening and tests and an excellent, comprehensive section on genetics of breast cancer. Last site update April 15, 2001. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

Cystic Fibrosis

Clinical description

Cystic fibrosis (CF) is caused by changes in a protein that controls the transfer of chloride and sodium ions (salts) across cell membranes. Disruption of salt transfer results in abnormal gland secretions and dehydration due to increased loss of salt and water during sweating. CF affects almost all of the glands in the body that secrete fluid, resulting in a variety of symptoms. Secretions may be thick and cause blockage in the pancreas, intestines and lungs. Mucus blockage also provides places for bacteria to multiply, increasing the probability of infection. CF children show poor digestion, dehydration, coughing and vomiting. As the disease progresses, teenagers show slowed growth, delayed puberty and reduced physical endurance. Adults show more serious complications such as collapsed lung, heart failure, infertility and frequent infections that eventually lead to death.



Genetics

Cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene on chromosome 7 which codes for the protein that controls ion transfer across cell membranes. Molecular analysis has identified approximately 100 mutations in the CFTR gene. Different mutations determine the severity of symptoms seen in CF patients.

Inheritance

Autosomal recessive.

Incidence

CF is the most common hereditary disease leading to death among Caucasian people in the United States. The incidence of the disorder is: 1 in 2,500 Caucasians; 1 in 14,000 blacks; 1 in 11,500 Hispanics; and 1 in 25,000 Asians

Diagnosis without genetic screening

Half of the patients with CF are undiagnosed during the first year of life and 25 percent remain undiagnosed by the end of the second year.

Clinical outcome without screening and treatment

If not diagnosed early, 13 percent of newborns and infants will die. Most untreated CF individuals will not live past their late 20's. In general, males live longer than females.

Clinical outcome with screening and treatment

If diagnosed and treated, newborn and infant mortality is reduced. Half of the people with CF live longer than 28 years due to availability of an increasingly wide range of treatments. These include physical therapy, enzyme replacements, supplemental salt, antibiotics to control infection, oxygen therapy, surgery and organ transplantation. Treatment for CF costs an average of $40,000 U.S. per year per patient in direct medical costs alone. Gene therapy is under investigation and evaluation.

Testing

Mutation in the CFTR gene results in an increase in an enzyme called trypsinogen. The initial newborn screen tests for this enzyme using a dried blood sample. However, this is not a conclusive test for CF. Measuring the salt levels in sweat can usually confirm the diagnosis.

Genetic counseling

Prenatal diagnosis is possible for most families. Carrier screening of the general population is possible using DNA mutation analysis. CF carrier testing is not recommended at this time unless a family history of CF is present. It is difficult to detect all carriers. Only 80 - 90 percent of carriers will be identified with the available tests. Newborn screening is recommended to prevent malnutrition as well as improve lung condition. Embryo screening for CF is available for carrier parents prior to embryo implantation during an in-vitro fertilization procedure.

Genetic Screening of Newborn Infants: What Should We Test And Why?

References

Cystic Fibrosis. In: *Merck Manual Home Edition online* (Chapter 43).
http://www.merck.com/pubs/mmanual_home/sec4/43.htm
The chapter from the Merck Manual Home Edition concerning cystic fibrosis. Explains the genetic basis of the disorder, symptoms and treatment. Last site update March 12, 1996. Accessed May 14, 2001.

CysticFibrosis.com
http://www.cysticfibrosis.com
Resource has daily living, associations and foundations, gene therapy and genetic testing. Also a great Just For Kids section. Last site update May 14, 2001. Accessed May 14, 2001.

Cystic Fibrosis Foundation
http://www.cff.org/
Contains up-to-date facts, research, publications, clinical trials, public policy and research center locations. Last site update May 14, 2001. Accessed May 14, 2001.

Cystic Fibrosis LISTSERV. Dalhousie University
http://www2.dal.ca/distsite/frank/cf.html
Information collected from LISTSERV@YaleVM.CI S.Yale.Edu, which is home of the CYSTIC-L mailing list. Contains basic information about CF, how it is diagnosed, why an individual gets CF and sources for further information. Last site update March 12, 1996. Accessed May 14, 2001.

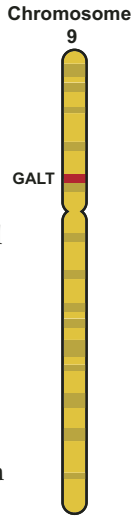
Genetic Testing for Cystic Fibrosis - National Institutes of Health Consensus Statement 1997
http://odp.od.nih.gov/consensus/cons/106/106_statement.htm
Reports current knowledge about genetic testing for cystic fibrosis in various populations including treatment costs. Discusses the circumstances in which cystic fibrosis should be tested for and directions for future research. Last site update September 1997. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

Galactosemia

Clinical description
Galactosemia is caused by the lack of an enzyme in the liver necessary for the breakdown of galactose. Galactose is the product of digested lactose, which is found in milk products. Symptoms include lethargy, diarrhea, vomiting, seizures, cataracts, susceptibility to infections, jaundice, mental retardation and liver disease.

Genetics
Galactosemia is caused by disruption of the galactose-1-phosphate uridyl transferase (GALT) gene on chromosome 9. More than 130 mutations in the GALT gene have been associated with galactosemia. Some mutations occur more commonly in particular ethnic groups and result in variable severity of the disorder.



Inheritance
Autosomal recessive.

Incidence
1 in 50,000 - 80,000 for classic galactosemia and 1 in 16,000 for other forms of galactosemia.

Diagnosis without genetic Screening
The symptoms of galactosemia appear early in infants, often leading to diagnosis. Jaundice, diarrhea, vomiting and failure to gain weight begin within a few days of milk ingestion. Cataracts appear within a few days of birth.

Clinical outcome without screening and treatment
If not detected early, galactosemia can result in severe liver disease and mental retardation. There is a high frequency of death at one to two weeks of age from severe bacterial infections.

Clinical outcome with screening and treatment
Galactosemia is treated by eliminating galactose and lactose from the diet throughout life. With prompt treatment, survival increases to close to 100 percent. A low IQ, learning disabilities and speech delays are often seen however, despite seemingly adequate treatment. This is thought to be due to an overrestrictive galactose-free diet. Galactosemic women rarely become pregnant due to ovarian failure. Although some clinical care and monitoring is involved, the cost for treatment of galactosemia is minimal in that it does not require a specially-formulated replacement diet.

Testing
This disorder can be detected by testing a blood sample for high levels of galactose or low GALT activity. Additional tests are often used to confirm the results.

Genetic counseling
Genetic counseling should be available for parents of infants identified as having galactosemia since it is important for these children to receive proper care and treatment. Treatment requires utilizing the services of specialized metabolic and genetic clinics that provide nutritional, psychological, nursing, biochemical and pediatric care. In addition, parents are usually unaware of this genetic disorder and require information in order to understand what needs to be done. Newborn screening programs generally have pamphlets and brochures to provide this information.

References
Galactosemia Resource
http://www.galactosemia.dynip.com/galactosemia/
Designed as an information resource and support group for galactosemic adults and parents of children with galactosemia. The overview section describes galactosemia and includes some more advanced genetic information. A useful feature of the site is the up-to-date articles section which includes news concerning newborn screening, emerging therapies and food ideas. Last site update May 14, 2001. Accessed May 14, 2001.

Parents of Galactosemic Children
http://www.galactosemia.org/
An excellent site with genetic information about this disorder, newborn screening updates and diet infor-

Genetic Screening of Newborn Infants: What Should We Test And Why?

mation. A unique feature of this site is the ability to e-mail the organization with questions for student reports or projects. Last site update May 8, 2001. Accessed May 14, 2001.

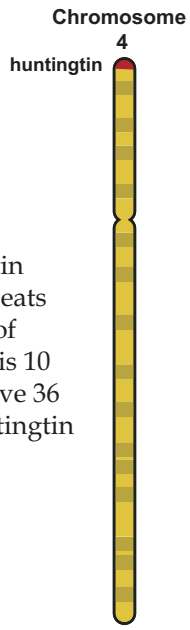
Texas Department of Health - Galactosemia Handbook
http://www.tdh.state.tx.us/newborn/handbook.htm
An easy-to-understand site designed for parents of children with galactosemia. Includes a general description of galactosemia giving inheritance and symptom information, followed by an easy-to-read, yet detailed, list of foods the galactosemic child should avoid. Last site update December 1999. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

Huntington's Disease

Clinical description

Huntington's disease is characterized by the progressive death of certain nerve cells in the brain. Symptoms generally appear between the ages of 35-40 years and include depression, mood swings, forgetfulness, involuntary twitching and lack of coordination. As the disease progresses, involuntary movements increase, memory declines, and walking, speaking and swallowing ability gradually diminish. Eventually affected persons are unable to care for themselves and death soon follows from choking, infections or heart failure. About 10 percent of patients have juvenile Huntington's disease, in which symptoms develop before age 20.



Genetics

Huntington's is caused by excessive repeating of the DNA bases CAG (trinucleotide repeats) in the huntingtin gene on chromosome 4. The more repeats an individual has, the earlier the age of onset. The normal number of repeats is 10 - 35. Huntington's disease patients have 36 - 121 repeats. The function of the huntingtin protein is not yet fully understood.

Inheritance

Autosomal dominant.

Incidence

1 in 20,000 Caucasians (except in Finland, where the incidence is much lower); 1 in 100,000 African Americans. 1 in 1,000,000 Africans; and 1 in 300,000 Asians.

Diagnosis without genetic screening

Symptoms are usually not observed before disease onset. Individuals with a family history of this disorder may show symptoms earlier.

Clinical outcome without screening and treatment

Involuntary movements and mental disturbances continue to increase.

Clinical outcome with screening and treatment

No cure is currently available for Huntington's disease. However, involuntary movements, rigidity and psychiatric symptoms can be suppressed or reduced with certain drugs. Neural and stem cell transplantation may be a potential option for treatment in the future.

Testing

The huntingtin gene is analyzed in a blood sample to determine the number of CAG repeats.

Genetic counseling

Genetic counseling is offered before and after testing to individuals who have a family history of Huntington's disease. Because this disorder shows dominant inheritance, a child with an affected parent has a 50 percent chance of inheriting the disorder. Some individuals may choose not to know their prognosis, rather than live with the knowledge that they have a disorder with no cure. Others would rather have a definitive diagnosis and choose to be tested. Personal life choices, such as decisions about childbearing, can be affected by test results. Genetic screening allows individuals to plan for their future and the future of their families. There are support groups for individuals who test positive for Huntington's and for their caregivers, which help to ease the distresses they must face.

References

Caring for People with Huntington's Disease
http://www.kumc.edu/hospital/huntingtons/
Maintained by the Department of Neurology at the Kansas University Medical Center. Information includes a description of Huntington's disease, specific care issues and a list of other Internet resources. An excellent feature of the site is a question and answer page for students writing school reports on the disorder. This page is constructed from questions students e-mailed to a doctor at the hospital. If the question isn't already addressed on the site students can e-mail questions about Huntington's Disease and receive answers within 1-2 days. Last site update February 23, 2001. Accessed May 14, 2001.

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Facing Huntington's Disease
http://neuro-chief-e.mgh.harvard.edu/mcmenemy/facinghd.html
A comprehensive online booklet from the Huntington's Disease Association. Organized chapters make information easy to find. Contains excellent information on medical and genetic components, dealing with diagnosis, youth risk and preparation for long-term illness. Last site update unknown. Accessed May 14, 2001.

Genetic Testing - Huntington's Disease
http://www.lib.uchicago.edu/~rd13/hd/testing.html
Discusses the pros and cons of being tested for the Huntington's gene for persons with a family history of Huntington's disease. Last site update November 3, 1996. Accessed May 14, 2001.

Huntington's Disease Information
http://www.lib.uchicago.edu/~rd13/hd/index.html
Contains an up-to-date list of links to documents concerning Huntington's disease on testing, research and family issues. Last site update May 12, 2000. Accessed May 14, 2001.

Huntington's Disease Society of America
http://www.hdsa.org
Identifies facilities by state where genetic testing is available for Huntington's disease. Also includes information on research, getting help and a common questions section. Last site update May 10, 2001. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

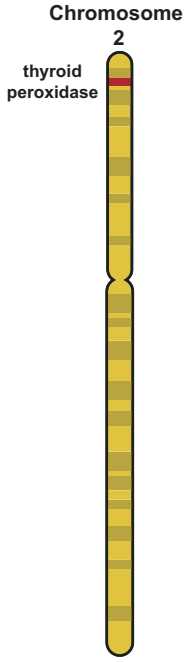
Hypothyroidism

Clinical description

Congenital hypothyroidism is one of the most common disorders detected by newborn screening. Infants with this disorder do not produce adequate amounts of thyroid hormone due to failure of the thyroid gland to develop properly. Thyroid hormone plays a vital role in normal growth, development and mental function in children. Although infants with hypothyroidism usually appear normal for up to three months after birth, early symptoms sometimes occur, including increased birth weight, puffy face, constipation and lethargy.

Genetics

In most newborns with hypothyroidism, there is no specific reason why the thyroid gland did not develop normally. However, about 10 - 20 percent of infants have an inherited form of the disorder, which is often characterized by visible enlargement of the thyroid gland (goiter). The most common inherited form of hypothyroidism is a defect in the thyroid peroxidase gene on chromosome 2. This gene plays an important role in the manufacture of thyroid hormone.



Inheritance

Autosomal recessive.

Incidence

1 in 4,000 overall; 1 in 12,000 African-Americans; 1 in 1,000 Hispanics; and 1 in 700 Native Americans.

Diagnosis without genetic screening

Affected infants may not show any symptoms. This can delay diagnosis of the disorder for up to three months, by which time brain damage is likely to have occurred.

Clinical outcome without screening and treatment

If not treated early, thyroid hormone deficiency causes mental retardation, delayed puberty, ataxia (loss of the ability to coordinate muscular movement), and stunted growth. Fifteen percent of individuals with untreated congenital hypothyroidism are institutionalized from age five to life; 25 percent require foster care from age five to 20; and 40 percent require adult care from age 20 for life.

Clinical outcome with screening and treatment

Hypothyroidism is treated by replacing the missing thyroid hormone through pills taken daily for life. The cost for a one-month supply is $10 - $20 U.S. Regular blood tests are needed to monitor hormone levels. If infants are treated early and treatment is followed properly, normal growth, intelligence and life span can be achieved.

Testing

Infants are screened 48 hours after birth using a dried blood sample obtained from a heel stick to detect thyroid hormone level. False positives may occur if the infant is tested prior to 48 hours, due to altered hormone levels caused by the stress of birth.

Genetic counseling

The family of a patient diagnosed with an inherited form of hypothyroidism is referred to a genetic counselor. Brochures for parents are provided by state newborn screening programs and are available before or after delivery. Additional information and counseling is available with a positive test.

References

American Academy of Pediatrics Section on Endocrinology and Committee on Genetics, and American Thyroid Association Committee on Public Health. Newborn Screening for Congenital Hypothyroidism: Recommended Guidelines. ***Pediatrics.*** **1993;91:1203-1209.**
http://www.aap.org/policy/04407.html
Contains an advanced clinical description of the disorder. Reviews screening programs for congenital hypothyroidism and differences in testing methods. Accessed May 14, 2001.

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Congenital hypothyroidism fact sheet. Riley Hospital for Children.
http://www.rileyhospital.org/document.jsp?locid=539
Discusses how hypothyroidism is detected in newborns, how often the disorder is genetic, how genetic cases are identified and treatment options. Last site update unknown. Accessed May 14, 2001.

Congenital hypothyroidism brochure. The MAGIC Foundation For Children's Growth.
http://www.magicfoundation.org/congthyr.html
Prepared for parents of children recently diagnosed with hypothyroidism. Contains easy-to-follow questions and answers about this disorder including symptoms, testing and treatment. Last site update 1998. Accessed May 14, 2001.

Genetic Screening of Newborn Infants: What Should We Test And Why?

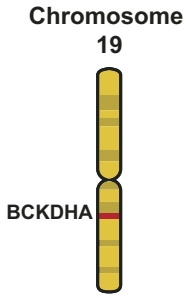
Maple Syrup Urine Disease (MSUD)

Clinical description

Individuals with maple syrup urine disease (MSUD) are unable to properly metabolize (break down) three amino acids - leucine, isoleucine and valine. These amino acids are present in all protein foods such as meat, eggs and milk. Smaller amounts are also found in cereals, vegetables and fruits. In individuals with MSUD the enzymes required to process these three amino acids are absent, inactive or only partially active. Because these amino acids do not get broken down completely, high levels accumulate in the blood, urine and sweat. The by-product of isoleucine has a characteristic sweet smell which gives the disorder its name. The three amino acids and their derivatives can be toxic at high levels and can lead to brain injury, mental retardation, seizures, vomiting, coma and even death.

Genetics

Defects in three genes on different chromosomes can lead to four types of MSUD. The most common type is classic MSUD which is caused by a defect in the BCKDHA gene on chromosome 19. In classic MSUD, enzyme activity is less than two percent of normal. The other variations are less severe.



Inheritance

Autosomal recessive.

Incidence

Classic MSUD occurs in 1 in 90,000 - 300,000 births and is seen in all ethnic groups worldwide. Incidence is 1 in 176 births in the Old Order Mennonites of Pennsylvania, United States.

Diagnosis without genetic screening

Without genetic screening, classic MSUD will only be diagnosed reliably after the first week of life. Three to four days after birth these infants show poor appetite, lethargy, irritability, the characteristic urine odor, boxing and pedaling limb movements and muscle rigidity and they emit a high-pitched cry. In children with less severe MSUD variants, symptoms may not appear until several months after birth.

Clinical outcome without screening and treatment

The severity of mental retardation that develops when MSUD is left untreated depends on the level of enzyme deficiency. Death occurs within the first two years of life in classic MSUD.

Clinical outcome with screening and treatment

MSUD is treated and managed very similarly to PKU or diabetes. Lifelong treatment beginning at the earliest possible age allows MSUD individuals to live a normal life span with normal intelligence. Treatment involves a carefully controlled diet to prevent the accumulation of the amino acids in the blood. The cost for special low-protein foods can be very high. For example, a box of crackers is about $16 U.S. An MSUD infant formula has been developed which provides all the vitamins and minerals necessary for proper development without leucine, isoleucine or valine. This can be supplemented with very small amounts of regular baby formula. Cost for this special formula is about $1,200 U.S. per month. Systems are available for frequent monitoring of amino acid levels and diet can be adjusted as needed. Some infants also can be helped with a thiamine supplement.

Testing

Newborn screening programs that test for MSUD use the same blood sample collected for PKU and galactosemia tests. Generally, blood is analyzed for elevated levels of leucine.

Genetic counseling

Information is available from U.S. state screening programs concerning dietary requirements. Counseling is available for the family of an identified individual. Carrier screening is also available for the Mennonites of eastern Pennsylvania.

Genetic Screening of Newborn Infants: What Should We Test And Why?

References

MSUD Family Support Group
http://www.msud-support.org
Includes information about the symptoms of MSUD, classification of disorder types, genetic testing and treatment options. Last site update unknown. Accessed May 14, 2001.

MSUD Webforum
http://neuro-www.mgh.harvard.edu/forum/MSUrineDiseaseMenu.htm
A webforum where individuals can post messages to discuss and comment on Maple Syrup Urine Disease. Last site update January 14, 2000. Accessed May 14, 2001.

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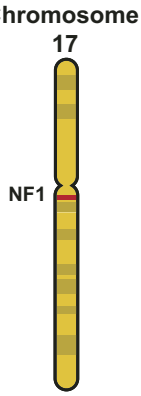
Neurofibromatosis 1

Clinical description

Neurofibromatosis 1 (NF1) is a genetic disorder that primarily affects the development and growth of cells in the nervous system. The disorder can cause neurofibromas (tumors to grow on nerves), freckling, cafe-au-lait spots (light brown spots on the skin), learning disabilities and bone deformities. The type and severity of symptoms shown by NF1 patients can vary widely, even between affected individuals from the same family.

Genetics



The NF1 gene, located on chromosome 17, produces a large and complex protein called neurofibromin. Scientists theorize that this protein acts as a switch to regulate cell growth.

Inheritance

Autosomal dominant. However, about 50 percent of cases are caused by spontaneous new mutations in the NF1 gene that occur in the sperm or egg prior to fertilization. This mutant allele can then be passed on to the individual's offspring.

Incidence

NF1 is one of the most common dominantly inherited genetic disorders with an incidence of 1 in 3,500 - 4000. The incidence of spontaneous mutations in the NF1 gene is 1 in 10,000. This is one of the highest known mutation rates for a disorder associated gene. The reason for this is currently under investigation, but may be due to the large size of the NF1 gene.

Diagnosis without genetic screening

It is often difficult to diagnose NF1 because the type and severity of symptoms are so different between patients. For example, one child might develop obvious signs of NF1 shortly after birth, while another person might live a lifetime without even knowing that he or she has the disorder. However, early diagnosis is possible without genetic screening by examining the patient for particular symptoms evident at an early age. Additional physical symptoms appear as children get older.

Clinical outcome without screening and treatment

Disfiguring, rarely cancerous skin tumors may develop, as well as bone deformation such as scoliosis (spinal curvature). Elevated blood pressure (hypertension) may develop in adults. The average life expectancy is reduced by at least 15 years overall.

Clinical outcome with screening and treatment

Treatment is currently designed to control symptoms. Surgery can be used to remove tumors in inconvenient areas such as belt and neck lines, but tumors may grow back and often in increased numbers. Back braces or surgery can be used to treat scoliosis. Learning disabilities may require educational intervention. Cancerous tumors (occurring in 3 - 5 percent of all cases) can be treated with surgery, radiation or chemotherapy. Medical care should be given by a physician familiar with the development of the disease.

Testing

Although genetic testing is available for NF1, it is rarely used to diagnose the disorder. The large size of the NF1 gene and the variety of mutations which can cause the disorder make identification of specific mutations in patients difficult. Testing is, however, more widely used for families with documented cases of NF1 where a specific mutation has been identified.

Genetic counseling

Genetic counseling may be requested by a couple affected by NF1 to assess risk of passing on the disorder to their child. Prenatal diagnosis is available in these cases, but often is not requested because the affected child may or may not develop severe complications from NF1.

References

The National Neurofibromatosis Foundation, Inc.
http://www.nf.org/
Site designed for patients and families by patients and scientists. Contains comprehensive information on NF1 and NF2 with symptoms and genetics. Last site update April 4, 2001. Accessed May 14, 2001.

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Neurofibromatosis Fact Sheet. National Institute of Neurological Disorders and Stroke.
http://www.ninds.nih.gov/health_and_medical/pubs/neurofibromatosis.htm
Contains a list of questions and answers about NF1 and NF2. Includes a section on prenatal genetic testing. Last site update January 27, 2000. Accessed May 14, 2001.

Neurofibromatosis, Inc.
http://www.nfinc.org/
NF, Inc. is an organization of independent state and regional chapters to provide support for NF families. Includes a description of NF, resources and current events section. Last site update April 29, 2001. Accessed May 14, 2001.

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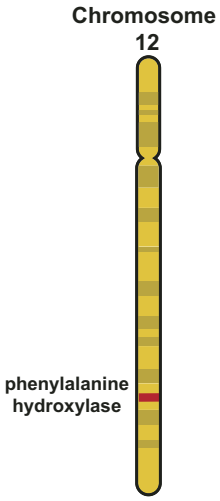
Phenylketonuria (PKU)

Clinical description
PKU is caused by the lack of an enzyme that processes the amino acid phenylalanine. Phenylalanine is present in all protein foods such as meat, eggs and milk. Smaller amounts are also found in cereals, vegetables and fruits. In PKU, phenylalanine is not broken down and accumulates in the blood. Phenylalanine is toxic to the brain. Untreated individuals with PKU show progressive developmental delay in the first year of life, mental retardation, seizures, autistic-like behavior and a peculiar body odor.



Genetics
In PKU individuals, the phenylalanine hydroxylase gene on chromosome 12 is disrupted. This gene encodes the protein that processes the amino acid phenylalanine to reduce its level in the body. When the gene is mutated, phenylalanine builds up in the body.

Inheritance
Autosomal recessive.

Incidence
1 in 10,000 - 25,000. Incidence in the United States is 1 in 16,000 live births.

Diagnosis without genetic screening
PKU is rarely diagnosed before 6 months of age. After this, mental retardation is apparent.

Clinical outcome without screening and treatment
Life expectancy is reduced. IQ is less than 50 in 95 percent of affected individuals. Convulsions and hyperactivity are common in untreated individuals. Sixty-four percent of individuals with untreated PKU are institutionalized from age five for life; 18 percent require foster care from age five to 20; and 36 percent require adult residential support services.

Clinical outcome with screening and treatment
PKU is treated by eliminating phenylalanine from the diet for life. Normal early growth and development are expected with early treatment. The normal range of intelligence is possible with optimal dietary control. Patients who do not follow the regulated diet have memory deficits and other mental problems. The cost for special, low-protein foods can be very high. For example, a box of crackers is about $16 U.S.

The issue of maternal PKU (the responsibility of PKU mothers to maintain their phenylalanine-free diets while pregnant) needs to be addressed by the medical profession and by individuals with PKU. High levels of maternal phenylalanine (present if a mother does not maintain her diet) can adversely affect the development of the fetus. This issue has only become a problem since the implementation of genetic testing for PKU. Previously, few PKU individuals had children of their own. Now, individuals diagnosed with PKU through newborn genetic screening can lead normal reproductive lives and therefore must address these issues.

Testing
The blood phenylalanine level can be measured using a spot of dried blood. The PKU test (the Guthrie test) was the first genetic screening test developed. Automated tests are now used in some screening programs. The timing of the test is important; the test should be completed after the first day and before the seventh day of life. If done too soon, low levels in the newborn can be masked by the presence of maternal phenylalanine, yielding a false-positive result.

Genetic counseling
Information is available from U.S. state screening programs and is often mandated by state regulations or laws. Counseling is available for the family of an identified individual.

References
National PKU News
http://205.178.182.34/
Site contains diet information, politics and legislation concerning PKU and PKU research. Last site update March 2001. Accessed May 14, 2001.

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PKU Resource Booklet for Families. The Montreal Children's Hospital.
http://www.mcgill.ca/pahdb/handout/handout.htm
Includes information about the genetics of PKU, consequences of the disorder, treatment through diet and a glossary. Last site update October 7, 1999. Accessed May 14, 2001.

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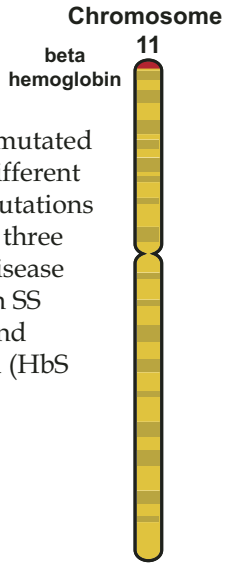
Sickle Cell Disease

Clinical description

Sickle cell disease describes a group of inherited disorders of red blood cells. Red blood cells are responsible for delivering oxygen to different parts of the body; normally they are round and contain a molecule called hemoglobin, which carries oxygen. If the gene encoding hemoglobin is mutated, it causes a change in the shape of the molecule. When the mutated hemoglobin delivers oxygen to the tissues, the red blood cell collapses, resulting in a long, flat sickle-shaped cell. These cells clog blood flow, resulting in a variety of symptoms including pain, increased infections, lung blockage, kidney damage, delayed growth and anemia (low blood cell count).

Genetics



The gene encoding the beta chain of the hemoglobin molecule, located on chromosome 11, can be mutated in a variety of ways that result in different types of sickle cell disease. Some mutations are more common than others. The three most common types of sickle cell disease in the United States are hemoglobin SS (Hb SS), hemoglobin SC (Hb SC), and hemoglobin sickle beta-thalassemia (HbS beta-thalassemia).

Inheritance

Autosomal recessive.

Incidence

Sickle cell disease affects more than 50,000 Americans. Although the disease occurs in high frequency in individuals of Mediterranean, Caribbean, Indian, Arab and Southeast Asian descent, the disease exhibits the highest frequency in people of African descent.

In African-Americans the incidence is 1 in 375 for HbSS, 1 in 835 for HbSC and 1 in 1,667 for HbS beta-thalassemia. In addition, 1 in 12 African-Americans are carriers for the disorder (have sickle cell trait). In United States populations, the prevalence of all types of sickle cell disease is equal to 1 in 58,000 Caucasians; 1 in 1,100 Hispanics (eastern states); 1 in 32,000 Hispanics (western states); 1 in 11,500 Asians; and 1 in 2,700 Native Americans.

Diagnosis without genetic screening

Clinical diagnosis is rarely made before 1 year of age, when symptoms lead to further investigation.

Clinical outcome without screening and treatment

Complications include increased infections, kidney damage, leg ulcers, bone damage and delayed growth. Ten percent mortality occurs in early infancy and childhood. Hospitalizations for sickle cell disease cost the U.S. government an estimated $475 million per year, at an average of $6,300 per hospitalization.

Clinical outcome with screening and treatment

With treatment, the incidence of early death is significantly reduced. When diagnosed, newborns are placed on penicillin until age six to prevent infections. Parents are educated in guidelines to follow with their child, including taking folic acid to make new red blood cells, drinking lots of water, avoiding extreme temperatures, and getting regular checkups with a physician.

Testing

Sickle cell diseases can be identified using isoelectric focusing of hemoglobin from filter paper blood spots.

Note: In the past, screening programs for sickle cell disease led to discrimination against individuals identified as being carriers for the disorder (having sickle cell trait). These individuals do not display the disorder but were treated as potentially ill, and often restricted from certain jobs and barred from joining the military. Problems that developed from the early sickle cell disease screening programs have resulted in regulations that govern current screening programs.

Genetic counseling

Genetic counseling is needed in order to provide rapid access to medical care for the affected individual. In addition, it is important to provide genetic counseling for carrier individuals in order to

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prevent any feelings of stigmatization or confusion about the meaning of their genetic status and so that they may make informed decisions about future offspring. Fears about confidentiality, discrimination in the work place, and insurability need to be addressed.

References

Ashley-Koch A., Yang Q., and Olney RS. Hemoglobin S allele and sickle cell disease. ***American Journal of Epidemiology.*** **2000;151:839-845.**

http://www.cdc.gov/genetics/hugenet/reviews/sickle.htm
This paper, available from the Center for Disease Control, provides some advanced information on the incidence of sickle cell disorder in certain populations. Last site update August 5, 1998. Accessed May 14, 2001.

Joint Center for Sickle Cell and Thalassemic Disorders
http://sickle.bwh.harvard.edu/menu_sickle.html
Contains comprehensive, detailed information about sickle cell disease. Covers hemoglobin, syndrome definitions and management considerations, including newborn screening programs. Also includes basic and clinical research. Last site update July 2, 1999. Accessed May 14, 2001.

Sickle Cell Information Center Home Page
http://www.emory.edu/PEDS/SICKLE/
An comprehensive site with information on sickle cell anemia, health care guidelines, teacher and student resources and interpreting newborn screening results. Also includes a useful Powerpoint presentation and sickle cell tutorial. Last site update April 2001. Accessed May 14, 2001.

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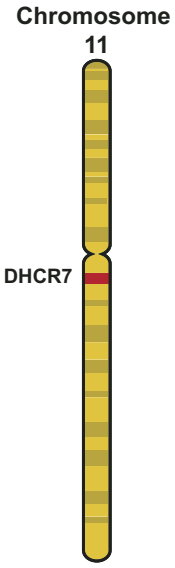
Smith-Lemli-Opitz (SLO/RSH) Syndrome

Clinical description

The first three cases of this disorder were described in 1964 in three families with surnames beginning with R, S, and H. The researchers (Smith, Lemli and Opitz) therefore called this syndrome "RSH."



Individuals with SLO/RSH syndrome are unable to make cholesterol, an essential nutrient required for proper development of cell membranes and the white matter of the brain. Because cholesterol is not provided to the developing fetus by the mother during pregnancy, symptoms develop before birth. As development continues after birth, lack of cholesterol can result in a variety of symptoms which vary in severity from individual to individual. Symptoms include growth retardation, developmental delay, feeding difficulties, behavioral problems and physical malformations such as small head, cleft palate, cataracts, drooping eyelids, extra (sixth) fingers or toes, webbing between the second and third toes, male genital malformations and heart defects.

Genetics

SLO/RSH syndrome results from a mutation in either the DHCR7 gene on chromosome 11 or the SLOS gene on chromosome 7. These genes code for essential enzymes required for the synthesis of cholesterol.

Inheritance

Autosomal recessive.

Incidence

SLO/ RSH syndrome occurs with relatively high frequency: 1 in 20,000 to 30,000 in Europe, the United States and Canada.

Diagnosis without genetic screening

General poor growth, developmental delay, and congenital malformations may prompt testing that leads to diagnosis.

Clinical outcome without screening and treatment

The affected person shows continued failure to thrive; and developmental delays lead to a limited life span. Prognosis is related to an individual's cholesterol levels: the lower the cholesterol level, the more severe the condition and the shorter the life-expectancy.

Clinical outcome with screening and treatment

Patients given cholesterol as infants or adults show improved growth, a lessening of behavioral problems and more rapid developmental progress. Although adults benefit from this treatment, the earlier cholesterol can be supplied, the better the eventual outcome. With correct diagnosis and treatment, many children can learn to walk, talk, and acquire basic living skills. Normal life span is possible with good care and nutrition.

Testing

Typically, testing occurs as a result of observing physical abnormalities. Females often go undiagnosed because they do not show the genital malformations seen in boys. A test for low levels of cholesterol and abnormally high levels of a cholesterol precursor is usually used to diagnose SLO/RSH. However, this test can be unreliable. DNA analysis for mutations of the DHCR7 gene is available on a limited basis. Prenatal testing is also available.

Genetic counseling

Parents need to be educated about the nature of this disorder to prevent them from overfeeding their children in an attempt to make them grow faster. They also need to monitor carefully the dietary formula given to the infant.

References

SLO/RSH Advocacy and Exchange
http://members.aol.com/slo97/index.html
Contains detailed information about diagnosis, natural history, biochemistry, genetics and treatment, as well as current disease research updates. Last site update July 1999. Accessed May 14, 2001.

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6. SAMPLE COLLECTION AND STORAGE

How are samples collected and analyzed?

Genetic tests can be carried out using a dried blood sample collected from a single heel prick. Currently, such samples are taken from all newborns before discharge from the hospital. For infants not born in a hospital, the doctor or midwife in charge must collect a blood sample. The sample is then sent to the laboratory for analysis. Some states have agreed to pool their tests into a single regional laboratory to economize. Other states contract the work out to private or public laboratories. In 1986, collection costs were estimated to be about $6 per sample. This includes the cost of drawing blood, administration, medical record keeping, supplies, billing and overhead.

Genetic tests performed with the sample of dried blood serve as an initial screen for a genetic disorder; they do not provide a diagnosis. To confirm a diagnosis, a physician must perform follow-up tests.

Quality control

Unfortunately, with vast numbers of samples being tested, mistakes can occur. These include misplaced samples, confusion among samples, incorrect labeling and incorrectly obtained samples. Such errors could result in a false negative or false positive screen.

The tests used for newborn screening should have several characteristics. Each test should have high sensitivity. That is, a test should yield very few false negative results, failure to detect the disorder in an affected individual. Similarly, a test should yield very few false positive results, which occur when the test erroneously detects the disorder in an unaffected individual. Ideally, a test would be 100 percent accurate, but this is not always the case. In large screening programs, the number of false negatives and false positives should be kept as low as possible. A test should also have high specificity. That is, tests must be specific for one particular disorder. A test should not incorrectly label individuals who have some other medical condition.

These quality control issues were addressed by the Centers for Disease Control with the Newborn Screening Quality Assurance Program (NSQAP). However, funding for this program ended in 1999 based on recognition of new screening methods, such as DNA-based testing, that require evaluation. Establishing a new mechanism for providing oversight and quality assurance in federally funded laboratories must be considered in developing a policy for newborn screening.

What happens to my samples after testing?

A special absorbent paper in the form of a card (Guthrie card) is used to collect the blood samples from newborns. Each card also contains information about the infant (and sometimes the mother) to be used for identification. Following screening, many programs retain the cards for various lengths of time to allow a repeat of the test when necessary. However, about 95 percent of infants will not need repeated tests.

Residual blood samples can be a useful resource. Stored sample cards can be used in:

- Research in developing new tests - determining the accuracy of new testing methods
- Public health research - determining the prevalence of certain genetic attributes in the general population
- Clinical or forensic investigations - information can be used in finding missing children or investigating a genetic condition which may have contributed to a child's death

Current national standards in the United States allow the use of sample cards for research without requiring an individual's consent, as long as identifying data are removed. Policy-makers considering sample storage must weigh concerns about privacy and confidentiality of genetic information against the benefits of valuable research opportunities. Newborn screening programs vary in how they deal with residual blood samples. Time of sample storage ranges from 21 years to one week in the United States. In Denmark, cards are stored indefinitely, while in France they are destroyed soon after testing.

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Policies also vary or are unclear concerning parent education about the use of residual blood samples, an individual's right to refuse usage of their sample, and ownership of the card. The state of Maryland provides parents with an informational brochure concerning the use of cards in research. No U.S. state requires individuals to give permission for the use of their genetic information in studies. Australia and New Zealand have a policy of "informed refusal" for sample storage (i.e. after being informed about possible uses of the sample, individuals can refuse to have it stored), and using the cards for purposes outside the screening program requires informed consent. Austria, Finland, Iceland, Sweden and Switzerland have enacted legislative policy to protect information gained from genetic testing.

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7. COST CONSIDERATIONS

How much should screening programs cost?

Note: All monetary amounts are in U.S. dollars unless otherwise indicated.

Individual states in the United States finance their newborn screening programs in different ways. Most set and collect fees for the program. Often, fees do not fully cover the cost, so public health system funding is used to supplement the program. Fees charged per newborn range from less than $15 to nearly $60. For 30 states, the testing fee includes the laboratory test as well as other services. Of these, 17 states finance more comprehensive services such as follow-up and treatment. Table 1 lists newborn screening costs for several countries and the United States.

Financing a screening program comes with an expectation that the benefits will equal or be greater than the cost. Many different estimates have been made to analyze the cost and benefit of screening programs. However, these calculations are controversial. Many object to the idea of human lives being represented by numbers. Others are uncertain what monetary values to assign. Nonetheless, the U.S. Congress Office of Technology Assessment (OTA) concluded that the net health care savings for the 100,000 infants screened in the United States in 1986 was $3.2 million and that the net health care savings per detected and treated case was $93,000. These calculations have been called into question by some, who point out that the OTA did not take into account monetary burdens of identified individuals and did not include the sickle cell disease test, which was being piloted in many states at that time. However, the OTA study did provide a good basis for evaluating basic costs. Today, the overall monetary benefit of newborn screening programs remains largely uncertain.

What should insurance cover?

For U.S. children with insurance, the Health Insurance Portability and Accountability Act offers protection for newborns in every state. This act was specifically designed to protect infants with genetic conditions formerly considered "pre-existing" under many health plans. Some states have enacted laws that require insurance companies to pay for special formula and nutrition supplements considered to be treatment for certain genetic disorders.

Medicaid is also an important source of coverage for children with disorders identified by newborn screening. Medicaid requires that each state provide services that are medically necessary for these infants.

For low-income children who are not eligible for Medicaid, Congress enacted Title XXI of the Social Security Act, which established the State Children's Health Insurance Plan (SCHIP). Each state can determine what benefits it covers under SCHIP. This may not always include the special therapies necessary for children with genetic disorders identified through its newborn screening program.

Considering what services to provide in addition to the genetic screening test itself and how these services may increase the cost is an important policy decision. Many feel that comprehensive care is essential for a screening program to be worthwhile. However, children with complex conditions requiring lifelong care will likely need treatment beyond the scope of any form of insurance. For many, the situation becomes even more difficult once adulthood is reached, when coverage through public programs is discontinued.

New technology could allow for more tests - at a price

Another cost consideration is the recent introduction of a new technology called "tandem mass spectrometry." The cost of a single machine can range from $250,000 to $400,000. It is estimated that adding this technique to screening programs would cost about $25 per infant. However, one machine can process about 500 specimens a day (allowing for speedy sample processing) and can test for many rare genetic disorders using blood from a single heel prick. Diseases that can be screened using tandem mass spectrometry are PKU, maple syrup urine disease and 30 other metabolic disorders not considered in this unit. Since not all states use this technology, newborns in some states are not being screened for all of the disorders that they would be if they lived in another

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state. Concerned about this disparity, some parents have resorted to purchasing testing kits from independent labs outside their state. Baylor University Medical Center in Dallas offers a $25 testing kit which can be ordered by mail and sent back to them for analysis by tandem mass spectrometry. Committees in some U.S. states are currently evaluating the pros and cons of using this technology. Implementing tandem mass spectrometry enabled Wisconsin to add 14 new disorders to their screening program. They estimate that adding these disorders will save the medical community, insurance companies and state programs up to $500,000 annually.

Table 1: Newborn screening program costs for sample states and countries (costs include screening test and follow-up)

State or Country	Cost of Newborn Screen	Number of Disorders Tested	Tandem Mass Spectrometry
California	$42	4	no
Illinois	$32	6	no
Kentucky	$14.50	4	no
Massachusetts	$49.55	10+20 optional	yes
New Jersey	$34	4	no
Ohio	$27	5	no
Washington	$39.25	4	no
Wisconsin	$59.50	21	yes
Australia	variable by region	4	yes (some regions)
Czech Republic	100 Czech Crowns (~$25 U.S.)	2	no
Denmark	160 DKK (~$19 U.S.)	4	in trial
New Zealand	14 NZ dollars (~$6 U.S.)	7	no
Switzerland	35 Swiss Francs~($20 U.S.)	5	no

The cost of adding new tests

The cost of each individual test must be minimal. Costs include running and maintaining the screening program as well as follow-up visits for infants who test positive, and their parents. The combined cost for PKU and hypothyroidism tests, which all U.S. states and many countries require, was about $6 in 1986. Several newborn screening programs also test for maple syrup urine disease (MSUD) and galactosemia. The cost of laboratory detection and follow-up for galactosemia and MSUD was about $1.50 per specimen in 1986. However, the recent advent of tandem mass spectrometry analysis may change how cost is calculated. If adding a new test to the screening program exceeds a base cost level, the additional expense needs to be justified by specific benefits.

Table 2 lists costs for genetic tests that are not included in all state or country programs. For most disorders, several laboratories can provide genetic testing.

The following factors should be considered when evaluating the quoted cost at a particular laboratory:

- Is the laboratory associated with a reputable company or university?
- Is the laboratory's work published in medical literature?
- What testing method is used? For example, tests for single gene mutations are less expensive than full gene sequencing. See American Academy of Pediatrics, Molecular Genetic Testing in Pediatric Practice: A Subject Review (December 2000) for information on specific testing methods.
- What testing strategy is used? Some labs test for a large number of mutations all at once. Others test first for the most common mutations, then proceed according to the results.
- How many individuals need to be tested? Several family members may need to be tested to obtain a meaningful test result.
- Can contractual agreements lower costs? Hospitals, insurers, and laboratories negotiate contracts to set the price of testing and amount of reimbursement. Contracts to establish large-scale screening efforts can lower costs substantially.

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Table 2: Costs of testing for selected genetic disorders

Disorder	Laboratory	Cost
Alpha-1-antitrypsin	Baylor College of Medicine, DNA Diagnostic Lab (Baylor)	$285
Alpha-1-antitrypsin	University of Florida	Testing kit available free from Alpha-1 Association
Alzheimer's disorder (APOE e4 mutation)	Athena Diagnostics	$279
Breast cancer (BRCA1/ BRCA2)	Baylor	$350 (only available for limited population)
Breast cancer (BRCA1/ BRCA2)	University of California, San Francisco, Clinical Molecular Diagnostics Lab (UCSF)	$354
Breast cancer (BRCA1/ BRCA2)	Myriad Genetics	$2580 (full gene sequencing)
Cystic fibrosis	Baylor	$145 (mutation only), $285 (family linkage analysis)
Cystic fibrosis	UCSF	$146 (31 mutations)
Cystic fibrosis	University of Colorado, DNA Diagnostic Lab (U. Co.)	$150 (carrier status based on family analysis), $300 (mutation analysis)
Cystic fibrosis	Comprehensive Genetic Services (CGS)	$50 (mutation analysis)
Galactosemia	Mayo Clinic, Biochemical Genetics Lab	$107 (enzyme assay), $250 (isoelectric focusing if enzyme assay is unclear)
Galactosemia	CGS	$198
Huntington's disease	Baylor	$285
Huntington's disease	UCSF	$325
Huntington's disease	U. Co.	$250
Huntington's disease	CGS	$175
Maple syrup urine disease	Baylor	$25 (As part of Supplemental Newborn Screening Program kit which also screens for 27 other disorders)
Neurofibromatosis 1	Boston University School of Medicine, Center for Human Genetics	$1250 (family linkage analysis for up to 4 people)
Neurofibromatosis 1	Children's Hospital, DNA Diagnostic Laboratory, Boston, MA	$415 (FISH analysis)
Neurofibromatosis 1	Laboratory Corporation of America	Protein assay only: $550 (if unknown mutation), $400 (if known mutation)
Sickle cell disease	Baylor	$285
Sickle cell disease	UCSF	$181
Sickle cell disease	CGS	$98
Smith-Lemli-Opitz syndrome	Boston University School of Medicine, Center for Human Genetics	$1250 (family linkage analysis for up to 4 people), $225 (analysis of one mutation)
Smith-Lemli-Opitz syndrome	Kennedy Krieger Institute, Baltimore, MA	$150

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8. LEGISLATION AND EXISTING LAWS

Legislation may need to be developed to address the sensitive issues involved in newborn screening. Issues such as preserving patient and family rights, deciding what tests to include in the screening program and ensuring privacy of genetic information may require new laws to be written as a policy consensus is reached.

What are my rights?

Genetic screening policies must consider the rights of the patient and the family. In many cases, legislative action is required to enforce newborn screening program policies concerning this issue. Legislators drafting and voting on these laws must consider questions such as: Should parents have the right to refuse screening for their newborn, and if so, under what circumstances? Should parents be provided with information about newborn screening, and if so, what language should it be in?

Informed consent

Informed consent is the right to say yes or no to screening after consideration of all available information. Supporters of the informed consent model argue that it is the best method of ensuring patient autonomy, an essential part of any medical procedure. They also feel that using informed consent increases patient awareness by helping parents understand why their newborn is being screened. However, some feel that certain genetic tests may be in the best interest of the child and that parents' objections should not hinder the screening process. They also argue that it is logistically difficult to obtain informed consent for newborn screening due to time constraints, varied birth settings and the large number of newborns to be screened.

The right to refuse genetic screening varies among U.S. states. For example, Wyoming requires parents to give written consent for newborn screening and Maryland has a voluntary newborn screening program. In most other states, genetic tests do not require parental consent. Although most states allow parental refusal, many require special justification such as religious reasons. In many cases, parents aren't informed that they have the right to refuse.

Informed consent policies also vary among western European countries. Austria and Sweden require fully informed consent for screening. Finland has a voluntary screening program. France has strict penalties for not obtaining informed consent. In Australia and New Zealand, participation in the newborn screening program is not mandatory. Germany currently has no regulatory legislation for genetic screening but is in the process of evaluating the need for informed consent. Many countries, like Germany, have not yet established policy guidelines or passed legislation to address issues in genetic screening.

Parental education

Policy makers need to consider the issue of how to provide educational material about screening programs to parents and health care providers. Most countries and U.S. states have not enacted legislation requiring educational materials for parents during newborn screening. Forty-nine U.S. states provide educational materials for parents. However, hospital practices regarding parental information may vary *within* those states. Only 13 states distribute the information *prior* to testing and in almost half of the states this information is only provided in English. Policies in most other countries are unclear about or do not address providing educational materials. However, Australia and New Zealand require that written information be provided for parents prior to testing.

Note: For detailed information about each U.S. state concerning informed consent and parental education, please refer to the journal article "Public Participation in Medical Policy-Making and the Status of Consumer, Autonomy: The Example of Newborn Screening Programs in the United States," listed in the References section.

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Existing laws

Some legislation has already been written dealing directly with newborn genetic screening. Here is a sampling:

United States

H.R. 4365 - Children's Health Act of 2000
Title XXVI - Screening for Heritable Disorders

Requires states to:

- Expand screening, counseling, testing and specialty services
- Improve systems of providing information and counseling on available therapies
- Improve access for medically under served populations
- Develop a plan for collection of outcome data
- Develop a plan for monitoring the quality of services
- Evaluate effectiveness of test accuracy using evidence-based methods
- Develop an advisory committee to develop policy in newborn screening

Became public law on October 17, 2000

H.R. 602 and S. 318 - Genetic Nondiscrimination in Health Insurance and Employment Act
(introduced in House of Representatives and Senate)
A bill to prohibit discrimination on the basis of genetic information with respect to health insurance.
This act was referred to the House Education and Workforce Committee and the Committee on Health, Education, Labor, and Pensions (February 13, 2001).

Public Law 100-578 - Clinical Laboratory Improvement Amendments (1988)
Regulations for quality assurance in clinical laboratories.
Recommendations were made in July 2000 by the Secretary's Advisory Committee on Genetic Testing to amend this law to directly address quality control in genetic testing laboratories. These recommendations are currently being evaluated by the Health Care Financing Administration and the Centers for Disease Control.

New Jersey Senate Bill No. 2245 - Expansion of number of disorders included in newborn screening program
This act would expand the New Jersey newborn screening program to include tests for maple syrup urine disease, cystic fibrosis and several other treatable genetic disorders. The act also ensures treatment for all identified individuals and allows the State Department of Health to charge a reasonable fee for the services. Information about the newborns gained from testing may only be used for program evaluation purposes and is otherwise kept confidential. The act requires intensive educational training for public health care workers concerning the genetic disorders tested for by the newborn screening program.
This act was referred to the New Jersey Senate Health Committee on March 26, 2001.

Pennsylvania House Bill 854 - Amending the 1996 Insurance Coverage Act
Amends the Insurance Coverage Act to require health insurance policies to provide coverage for specially prepared, low-protein modified food products for the treatment of PKU and galactosemia. Coverage would be limited to $2,500 for an insured individual for any continuous period of 12 months.
This bill was passed October 18, 1999.

Note: To review laws concerning newborn screening for other states in the United States, see the Law Librarian's Society Legislative Source Book at http://www.llsdc.org/sourcebook/state-leg.htm. Links are provided for each state's code, statutes, laws and/or regulations. Most state law databases are searchable.

Other Countries

Austria - The Gene Technology Act (Law BGB 510/1994) Part IV

- Requires informed consent for screening
- Staff performing screen must be adequately qualified
- Data gained from screen is strictly protected
- Genetic counseling must be carried out before and after screening and must include psychological and social aspects

France - Laws No 94-653 of July 29, 1994 on respect for the human body
Genetic screening information can only be used for scientific purposes and requires full informed consent.

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The Netherlands - The Population Screening Act, 1992 (1996)
Screening for serious disorders for which there is no treatment and cancer is not allowed without ministerial approval.

Norway - Act Relating to the Application of Biotechnology in Medicine, Law n. 56 (1994)

- Comprehensive genetic counseling is provided before and after screening for presymptomatic disorders
- Genetic results may be communicated without restrictions between authorized medical institutions except for presymptomatic individuals or carriers
- Inquiring whether a test has been performed is restricted

Sweden - Law 114 of March 1991 on the Use of Certain Gene Technologies within the Context of General Medical Examinations (1993)
Authorization from the body is required before DNA testing can be carried out.

Switzerland - The Swiss Federal Contribution, 1992
Article 119 paragraph 2 states that the genetic make-up of an individual may be investigated, registered or divulged only with consent.

The United Kingdom - Privacy Amendment (Private Sector) Bill 2000
Information derived from individuals using genetic technologies requires consent to the extent that it identifies the individual.

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9. DEMOGRAPHICS AND DISORDER VARIABILITY

How can demographic data influence policy decisions?

Demographics is the study of population statistics. Demographic data are useful when considering public medical policies because some genetic disorders are more common among particular racial or ethnic populations. Examples of variable incidence among populations are listed below.

Alpha-1-antitrypsin
This disorder is predominantly found in populations of Caucasian descent, although some mutants alleles are present in African-Americans.

Alzheimer's disease -- APOE e4 allele
Not all ethnic backgrounds show a relationship between the APOE e4 allele and Alzheimer's disease. The APOE e4 allele has not been linked to Alzheimer's in Australian aborigines, sub-Saharan Africans and some Native Americans.

Breast cancer susceptibility genes -- BRCA1 and BRCA2
Disease-related mutations in these two genes are more common in Ashkenazi Jews than in other ethnic groups. Three specific mutations in the two BRCA genes are present in approximately 2.5 percent of this population. It is estimated that 20 - 25 percent of all breast cancers in women of Ashkenazi Jewish descent result from one of these mutations.

Cystic fibrosis (CF)
This disorder is more common among Caucasians with Northern European ancestry (1 in 2,500). It is uncommon in Asians (1 in 25,000), Hispanics (1 in 11,500) and blacks (1 in 14,000). The Irish Republic has the highest incidence in the world (1 in 1,500).

Galactosemia
Although galactosemia occurs in all ethnic groups worldwide, some mutations cause a less severe phenotype and are more prevalent in particular ethnic groups, such as African-Americans. In Japan, classic galactosemia is not as frequent as it is in Caucasian populations in the United States.

Huntington's disease
Huntington's disease is less common in populations in Japan, China, Finland and African blacks than in those of western European descent. Huntington's affects 1 in 20,000 Caucasians, 1 in 100,000 black Americans, 1 in 1,000,000 Africans, and 1 in 300,000 Asians.

Hypothyroidism
This disorder affects 1 in 4,000 people worldwide. Hypothyroidism is most frequently found in Hispanic (1 in 1,000) and Native American (1 in 700) populations. It is less frequent in African-Americans (1 in 12,000).

Maple syrup urine disease
This disorder is rare, occurring in 1 in 90,000 - 300,000 births in all ethic populations worldwide. It is most frequent in the Mennonites of Pennsylvania, U.S. (1 in 176).

Neurofibromatosis 1 (NF1)
The overall incidence of this disorder is 1 in 3,500 - 4000. NF1 is more common in Israeli (1 in 1000), North African (1 in 550) and Asian (1 in 1,000) populations. NF1 is less common in European and Caucasian populations (1 in 1,500).

Phenylketonuria(PKU)
PKU affects 1 in 6,000 - 10,000 individuals of European descent compared with 1 in 60,000 Ashkenazi Jews, African Americans or Asians.

Sickle cell disease
Sickle cell disorders are most common among individuals of African descent (1 in 375 - 1,667). The disorder is also commonly found in people of Mediterranean, Caribbean, Central and South American, Arabian and East Indian descent. In the United States, sickle cell disorders affect: 1 in 58,000 Caucasians; 1 in 1,100 Hispanics from Eastern states; 1 in 32,000 Hispanics from Western states; 1 in 11,500 Asians; and 1 in 2,700 Native Americans.

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Smith-Lemli-Opitz (SLO/RSH) syndrome
This disorder affects 1 in 20,000 - 30,000 in Europe, the United States and Canada. People with northern European ancestry have a higher frequency of the disorder while people of Asian or African descent have a lower frequency.

Populations differ

Each state, region and country has a different composition of racial and ethnic groups. Tables 1-6 illustrate the varied composition of populations in the United States, Canada and the United Kingdom.

These figures are based on 2000 state population estimates from the U.S. Government Census Bureau, 2001 Canadian Census from Statistics Canada and 2001 data from the United Kingdom Office for National Statistics Census Division. Note: percentages do not always add to 100 percent, due to different counting methods.

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Table 1: Population totals for United States (2000), Canada (2001) and United Kingdom (2001)

United States	281,421,906
Alabama	4,447,100
Alaska	626,932
Arizona	5,130,632
Arkansas	2,673,400
California	33,871,648
Colorado	4,301,261
Connecticut	3,405,565
Delaware	783,600
District of Columbia	572,059
Florida	15,982,378
Georgia	8,186,453
Hawaii	1,211,537
Idaho	1,293,953
Illinois	12,419,293
Indiana	6,080,485
Iowa	2,926,324
Kansas	2,688,418
Kentucky	4,041,769
Louisiana	4,468,976
Maine	1,274,923
Maryland	5,296,486
Massachusetts	6,349,097
Michigan	9,938,444
Minnesota	4,919,479
Mississippi	2,844,658
Missouri	5,595,211
Montana	902,195
Nebraska	1,711,263
Nevada	1,998,257
New Hampshire	1,235,786
New Jersey	8,414,350
New Mexico	1,819,046
New York	18,976,457
North Carolina	8,049,313
North Dakota	642,200
Ohio	11,353,140
Oklahoma	3,450,654
Oregon	3,421,399
Pennsylvania	12,281,054
Rhode Island	1,048,319
South Carolina	4,012,012
South Dakota	754,844
Tennessee	5,689,283
Texas	20,851,820
Utah	2,233,169
Vermont	608,827
Virginia	7,078,515
Washington	5,894,121
West Virginia	1,808,344
Wisconsin	5,363,675
Wyoming	493,782
Puerto Rico	3,808,610
Canada	30,007,094
Newfoundland and Labrador	512,930
Prince Edward Island	135,294
Nova Scotia	908,007
New Brunswick	729,498
Quebec	7,237,479
Ontario	11,410,046
Manitoba	1,119,583
Saskatchewan	978,933
Alberta	2,974,807
British Columbia	3,907,738
Yukon Territory	28,674
Northwest Territories	37,360
Nunavut	26,745
United Kingdom	58,789,194

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Table 2: Asian population totals for United States (2000), Canada (2001) and United Kingdom (2001)

Region	Total Asian Population	% of population that is Asian
United States	10,242,998	3.6
Hawaii	503,868	41.6
California	3,697,513	10.9
New Jersey	480,276	5.7
New York	1,044,976	5.5
Washington	322,335	5.5
Nevada	90,266	4.5
Alaska	25,116	4.0
Maryland	210,929	4.0
Massachusetts	238,124	3.8
Virginia	261,025	3.7
Illinois	423,603	3.4
Oregon	101,350	3.0
Minnesota	141,968	2.9
Texas	562,319	2.7
District of Columbia	15,189	2.7
Connecticut	82,313	2.4
Rhode Island	23,665	2.3
Colorado	95,213	2.2
Georgia	173,170	2.1
Delaware	16,259	2.1
Arizona	92,236	1.8
Pennsylvania	219,813	1.8
Michigan	176,510	1.8
Kansas	46,806	1.7
Florida	266,256	1.7
Utah	37,108	1.7
Wisconsin	88,763	1.7
North Carolina	113,689	1.4
Oklahoma	46,767	1.4
New Hampshire	15,931	1.3
Nebraska	21,931	1.3
Iowa	36,635	1.3
Louisiana	54,758	1.2
Ohio	132,633	1.2
Missouri	61,595	1.1
New Mexico	19,255	1.1
Tennessee	56,662	1.0
Indiana	59,126	1.0
Idaho	11,889	0.9
South Carolina	36,014	0.9
Vermont	5,217	0.9
Arkansas	20,220	0.8
Kentucky	29,744	0.7
Maine	9,111	0.7
Alabama	31,346	0.7
Mississippi	18,626	0.7
South Dakota	4,378	0.6
North Dakota	3,606	0.6
Wyoming	2,771	0.6
West Virginia	9,434	0.5
Montana	4,691	0.5
Puerto Rico	7,960	0.2
Canada	2,737,190	9.1
Alberta	234,835	8.0
British Columbia	729,915	18.9
Manitoba	61,320	5.6
New Brunswick	3,370	0.5
Ontario	1,384,835	12.3
Québec	191,530	2.7
Saskatchewan	17,755	1.8
Nova Scotia	7,840	0.9
United Kingdom	495,067	0.8

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Table 3: Native American population totals for United States (2000) and Canada (2001)

Region	Total Native American Population	% of population that is Native American
United States	2,475,956	0.9
Alaska	98,043	15.6
New Mexico	173,483	9.5
South Dakota	62,283	8.3
Oklahoma	273,230	7.9
Montana	56,068	6.2
Arizona	255,879	5.0
North Dakota	31,329	4.9
Wyoming	11,133	2.3
Washington	93,301	1.6
Idaho	17,645	1.4
Utah	29,684	1.3
Nevada	26,420	1.3
Oregon	45,211	1.3
North Carolina	99,551	1.2
Minnesota	54,967	1.1
Colorado	44,241	1.0
California	333,346	1.0
Kansas	24,936	0.9
Wisconsin	47,228	0.9
Nebraska	14,896	0.9
Arkansas	17,808	0.7
Michigan	58,479	0.6
Louisiana	25,477	0.6
Texas	118,362	0.6
Maine	7,098	0.6
Alabama	22,430	0.5
Rhode Island	5,121	0.5
Missouri	25,076	0.4
New York	82,461	0.4
Mississippi	11,652	0.4
Vermont	2,420	0.4
Puerto Rico	13,336	0.4

Region	Total Native American Population	% of population that is Native American
Delaware	2,731	0.3
South Carolina	13,718	0.3
Florida	53,541	0.3
Iowa	8,989	0.3
District of Columbia	1,713	0.3
Virginia	21,172	0.3
Hawaii	3,535	0.3
Maryland	15,423	0.3
Connecticut	9,639	0.3
Tennessee	15,152	0.3
Georgia	21,737	0.3
Indiana	15,815	0.3
Illinois	31,006	0.2
New Hampshire	2,964	0.2
Massachusetts	15,015	0.2
New Jersey	19,492	0.2
Ohio	24,486	0.2
Kentucky	8,616	0.2
West Virginia	3,606	0.2
Pennsylvania	18,348	0.1
Canada	952,890	3.2
Alberta	153,240	5.2
British Columbia	164,535	4.3
Manitoba	147,980	13.4
New Brunswick	16,110	2.2
Ontario	182,970	1.6
Québec	77,100	1.1
Saskatchewan	128,570	13.3
Nova Scotia	16,455	1.8

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Table 4: Black population totals for United States (2000), Canada (2001) and the United Kingdom (2001)

Region	Total Black Population	% of population that is Black
United States	34,658,190	12.3
District of Columbia	343,312	60.0
Mississippi	1,033,809	36.3
Louisiana	1,451,944	32.5
South Carolina	1,185,216	29.5
Georgia	2,349,542	28.7
Maryland	1,477,411	27.9
Alabama	1,155,930	26.0
North Carolina	1,737,545	21.6
Virginia	1,390,293	19.6
Delaware	150,666	19.2
Tennessee	932,809	16.4
New York	3,014,385	15.9
Arkansas	418,950	15.7
Illinois	1,876,875	15.1
Florida	2,335,505	14.6
Michigan	1,412,742	14.2
New Jersey	1,141,821	13.6
Texas	2,404,566	11.5
Ohio	1,301,307	11.5
Missouri	629,391	11.2
Pennsylvania	1,224,612	10.0
Connecticut	309,843	9.1
Indiana	510,034	8.4
Puerto Rico	302,933	8.0
Oklahoma	260,968	7.6
Kentucky	295,994	7.3
Nevada	135,477	6.8
California	2,263,882	6.7
Kansas	154,198	5.7
Wisconsin	304,460	5.7
Massachusetts	343,454	5.4
Rhode Island	46,908	4.5
Nebraska	68,541	4.0

Region	Total Black Population	% of population that is Black
Colorado	165,063	3.8
Minnesota	171,731	3.5
Alaska	21,787	3.5
Washington	190,267	3.2
West Virginia	57,232	3.2
Arizona	158,873	3.1
Iowa	61,853	2.1
New Mexico	34,343	1.9
Hawaii	22,003	1.8
Oregon	55,662	1.6
Utah	17,657	0.8
Wyoming	3,722	0.8
New Hampshire	9,035	0.7
South Dakota	4,685	0.6
North Dakota	3,916	0.6
Maine	6,760	0.5
Vermont	3,063	0.5
Idaho	5,456	0.4
Montana	2,692	0.3
Canada	662,215	2.2
Alberta	25,425	0.9
British Columbia	18,645	0.5
Manitoba	10,530	1.0
New Brunswick	2,515	0.3
Ontario	376,370	3.3
Québec	139,870	2.0
Saskatchewan	3,355	0.3
Nova Scotia	15,415	1.7
United Kingdom	1,617,029	2.8

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Table 5: Hispanic population totals for United States (2000) and Canada (2001)

Region	Total Hispanic Population	% of population that is Hispanic
United States	35,305,818	12.5
Puerto Rico	3,762,746	98.8
New Mexico	765,386	42.1
California	10,966,556	32.4
Texas	6,669,666	32.0
Arizona	1,295,617	25.3
Nevada	393,970	19.7
Colorado	735,601	17.1
Florida	2,682,715	16.8
New York	2,867,583	15.1
New Jersey	1,117,191	13.3
Illinois	1,530,262	12.3
Connecticut	320,323	9.4
Utah	201,559	9.0
Rhode Island	90,820	8.7
Oregon	275,314	8.0
Idaho	101,690	7.9
District of Columbia	44,953	7.9
Washington	441,509	7.5
Hawaii	87,699	7.2
Kansas	188,252	7.0
Massachusetts	428,729	6.8
Wyoming	31,669	6.4
Nebraska	94,425	5.5
Georgia	435,227	5.3
Oklahoma	179,304	5.2
Delaware	37,277	4.8
North Carolina	378,963	4.7
Virginia	329,540	4.7
Maryland	227,916	4.3
Alaska	25,852	4.1
Wisconsin	192,921	3.6
Indiana	214,536	3.5
Michigan	323,877	3.3

Region	Total Hispanic Population	% of population that is Hispanic
Arkansas	86,866	3.2
Pennsylvania	394,088	3.2
Minnesota	143,382	2.9
Iowa	82,473	2.8
Louisiana	107,738	2.4
South Carolina	95,076	2.4
Tennessee	123,838	2.2
Missouri	118,592	2.1
Montana	18,081	2.0
Ohio	217,123	1.9
Alabama	75,830	1.7
New Hampshire	20,489	1.7
Kentucky	59,939	1.5
South Dakota	10,903	1.4
Mississippi	39,569	1.4
North Dakota	7,786	1.2
Vermont	5,504	0.9
Maine	9,360	0.7
West Virginia	12,279	0.7
Canada	216,980	0.7
Alberta	18,745	0.6
British Columbia	23,885	0.6
Manitoba	4,775	0.4
New Brunswick	425	0.1
Ontario	106,835	0.9
Québec	59,520	0.8
Saskatchewan	2,005	0.2
Nova Scotia	520	0.1

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Table 6: Caucasian population totals for United States (2000), Canada (2001) and the United Kingdom (2001)

Region	Total Caucasian Population	% of population that is Caucasian
United States	211,460,626	75.1
Maine	1,236,014	96.9
Vermont	589,208	96.8
New Hampshire	1,186,851	96.0
West Virginia	1,718,777	95.0
Iowa	2,748,640	93.9
North Dakota	593,181	92.4
Wyoming	454,670	92.1
Idaho	1,177,304	91.0
Montana	817,229	90.6
Kentucky	3,640,889	90.1
Nebraska	1,533,261	89.6
Minnesota	4,400,282	89.4
Utah	1,992,975	89.2
Wisconsin	4,769,857	88.9
South Dakota	669,404	88.7
Indiana	5,320,022	87.5
Oregon	2,961,623	86.6
Kansas	2,313,944	86.1
Pennsylvania	10,484,203	85.4
Rhode Island	891,191	85.0
Ohio	9,645,453	85.0
Missouri	4,748,083	84.9
Massachusetts	5,367,286	84.5
Colorado	3,560,005	82.8
Washington	4,821,823	81.8
Connecticut	2,780,355	81.6
Puerto Rico	3,064,862	80.5
Tennessee	4,563,310	80.2
Michigan	7,966,053	80.2
Arkansas	2,138,598	80.0
Florida	12,465,029	78.0
Oklahoma	2,628,434	76.2
Arizona	3,873,611	75.5
Nevada	1,501,886	75.2
Delaware	584,773	74.6
Illinois	9,125,471	73.5
New Jersey	6,104,705	72.6
Virginia	5,120,110	72.3
North Carolina	5,804,656	72.1
Alabama	3,162,808	71.1
Texas	14,799,505	71.0
Alaska	434,534	69.3
New York	12,893,689	67.9
South Carolina	2,695,560	67.2
New Mexico	1,214,253	66.8
Georgia	5,327,281	65.1
Maryland	3,391,308	64.0
Louisiana	2,856,161	63.9
Mississippi	1,746,099	61.4
California	20,170,059	59.5
District of Columbia	176,101	30.8
Hawaii	294,102	24.3
Canada	24,618,250	82.0
Alberta	2,452,150	83.4
British Columbia	2,859,400	73.9
Manitoba	867,620	78.6
New Brunswick	693,640	96.4
Ontario	8,912,260	79.0
Québec	6,521,675	91.5
Saskatchewan	806,420	83.7
Nova Scotia	845,305	94.2
United Kingdom	54,153,898	92.1

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10. GLOSSARY

This glossary provides simple definitions of some of the more widely used terms in the Newborn Genetic Testing Unit.

allele: different forms of the same gene.

amino acid: any of 20 molecules which are the building blocks of proteins.

Ashkenazi: Jews who settled in middle and northern Europe and their descendants. There are roughly 11.2 million Ashkenazi Jews, constituting more than 80 percent of all Jews in the world.

autosomal: refers to inheritance related to any chromosome, except a sex chromosome.

carrier: an individual who is heterozygous, with one recessive allele.

chromosome: one of the threadlike "packages" of 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 mother and half from their father.

congenital: condition existing at, and usually before, birth. Refers to conditions that are present at birth, regardless of their cause.

demographics: the study of population statistics relating to certain factors such as ethnicity, age or income.

dominant: an allele 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 allele, the chance of passing on the allele (and therefore the disease) to children is 50-50 in each pregnancy.

DNA: the chemical inside the nucleus of a cell that carries the genetic instructions for making living organisms.

DNA markers: Identifiable physical locations on chromosomes whose inheritance can be monitored. Markers can be genes or some segment of DNA with no known coding function but whose pattern of inheritance can be determined.

DNA sequencing: a lab technique used to determine the order of nucleotide bases (A, C, G, and T) in a DNA molecule or fragment.

enzyme: any of several types of proteins that are produced by cells and act to initiate or accelerate specific biochemical reactions.

false negative: a test result that is read as negative when it is really positive.

false positive: a test result that is read as positive when it is really negative.

familial linkage analysis: analysis using blood or tissue samples from the patient and several of his or her relatives. The DNA of affected and unaffected relatives is extracted from the blood and analyzed to determine which DNA sequences are most likely to represent markers for a particular allele associated with a genetic disorder. The patient's DNA is then examined for the presence of these DNA markers.

FISH (fluorescence in situ hybridization) analysis: use of a fluorescent probe that binds to specific segments of DNA or RNA in chromosomes, allowing visualization of that segment, if it is present.

gene: the hereditary unit of DNA that occupies a certain spot on a chromosome, has a specific effect on the phenotype, and can mutate to various allelic forms.

genetic counseling: the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions.

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genetic disorder: physical or mental symptoms which are correlated with a mutation or mutations in one or more genes. Even when a person has inherited the underlying genetic makeup associated with a particular genetic disorder, symptoms may develop later in life or sometimes not at all.

gene therapy: an experimental technique in which a normal gene is inserted into a patient to correct a genetic disorder.

genotype: the genetic make-up of an organism, usually with respect to one or a few genes relevant in a particular context.

heterozygous: having two different alleles of the same gene.

homozygous: having two identical alleles of the same gene.

immunoassay: a test to determine the presence or absence of a particular type of biological substance based on a reaction with specific antibodies.

incidence: the frequency at which a genetic disorder is present in a population.

inheritance: transmitted through genes from parents to offspring. For example, "autosomal dominant" inheritance refers to an allele that is found on an autosomal chromosome and that is expressed in the phenotype in a dominant manner.

isoelectric focusing (IEF): a laboratory technique in which proteins are exposed to an electric current which causes them to move through a loose gel-like substance, thereby separating the different proteins. The relative distance a particular protein moves depends on its relative charge.

isoforms: different forms of proteins specific to particular tissues. When the proteins are enzymes, the term "isoenzyme" is generally used instead.

morbidity: displaying the symptoms of disease.

mortality: subject to death.

mutation: a permanent structural alteration in DNA, such as a deletion of a particular DNA subunit or a rearrangement of part of a chromosome. Mutations are the basis of genetic disorders.

onset: in genetics, time at which symptoms of a genetic disorder appear.

phenotype: the observable characteristics of an organism resulting from its genotype and environment.

public policy: a general plan of action or intent that is decided by a group of citizens or a government body.

recessive: a mode of inheritance in which a particular allele will be not be expressed in the phenotype if a different allele is present. The phenotype associated with the recessive allele will only be expressed if an individual has two copies of that allele.

sex-linked: a genetic trait in which the associated gene or genes are located on one of the sex chromosomes (X or Y). Sex-linked traits differ in their occurrence in males and females.

sensitivity: measure for assessing the results of diagnostic and screening tests. Sensitivity represents the proportion of persons in a screened population who really have a specific disorder and who were also correctly diagnosed as having the disorder by the test. It is a measure of the probability of correctly diagnosing a condition.

specificity: measure for assessing test results specific for one particular disorder. Specificity represents the proportion of people tested who had the medical condition the test was designed to diagnose and were not incorrectly diagnosed as having some other medical condition.

screening (genetic): the act of testing whole populations for particular genetic conditions or disorders.

Genetic Screening of Newborn Infants: What Should We Test And Why?

tandem mass spectrometry: a method used to determine the structure of complicated molecules using two mass spectrometers in series connected by a chamber that can break a molecule into pieces. For newborn screening, the molecules in a blood sample are "sorted" and "weighed" in the mass spectrometer. The information gained from sorting and weighing can be used to analyze compounds in the blood sample that have diagnostic significance.

task force: a committee of people assigned to address a particular topic. Members of a task force often represent a variety of difference backgrounds or expertise.

treatment: to control or reduce symptoms of a disorder.

Genetic Screening of Newborn Infants: What Should We Test And Why?

11. REFERENCES

For further resources on the following topics, please see *Additional Resources* at :
http://gslc.genetics.utah.edu/units/disorders/newborn/

Topics:

Human Genetics and Newborn Screening
Policy Issues
Medical Information on Genetic Disorders
- General
- Alpha-1-antitrypsin
- Alzheimer's Disorder
- Breast Cancer
- Cystic Fibrosis
- Galactosemia
- Huntington's Disease
- Maple Syrup Urine Disease
- Hypothyroidism
- Neurofibromatosis 1
- Phenylketonuria (PKU)
- Smith-Lemli Opitz Syndrome
- Sickle Cell Disease

Cost Considerations
Laboratory Websites with Specific Fee Information
Legislative Considerations and Existing Laws
Demographics