Newborn Screening Fact Sheets

Committee on Genetics

These newborn screening fact sheets were developed by the Committee on Genetics of the American Academy of Pediatrics (AAP) with considerable assistance and consultation from many individuals. It is hoped that the information contained in these fact sheets will assist the pediatrician in understanding the individual tests, their characteristics, and their strengths and weaknesses. Newborn screening is an individual function of each state; therefore, screening programs are not uniform throughout the United States (Table). Because the test results can affect children and parents in a variety of ways, there are special concerns about how states make decisions to adopt new tests and how they evaluate their current screening panels. Currently, many states are examining their practices. The information in the fact sheets was not designed to advocate specific newborn screening tests but to assist pediatricians in evaluating policies and procedures and in developing appropriate positions based on the needs of their patients and their geographic regions.

Confirmation of positive newborn screening test results is always necessary. Additionally, newborn screening programs should not preclude the pediatrician’s assessment of clinical symptoms at any age. Some disorders (eg, galactosemia and maple syrup urine disease) may become symptomatic before the availability of the results of newborn screening and may warrant specific testing when clinically suspected. Furthermore, although newborn screening tests are designed to detect infants with metabolic illnesses, certain tests may also identify carriers (ie, heterozygotes) or individuals with variants who may be clinically asymptomatic. Such information is important for the family because of the identification of “carrier couples.” This can have an impact on future pregnancies and other family members. Thus, the pediatrician needs to be aware of this aspect of newborn screening and provide appropriate counseling or referral of such families.

False-negative test results may occur for a variety of reasons. Pediatricians should be knowledgeable about the procedures used in their state programs and be aware of those groups of infants likely to be missed through screening (ie, those born prematurely, those who have received blood transfusions, those out-of-state or out-of-country births, and those who underwent testing too early). Under such circumstances, follow-up testing may be required for certain infants even if the newborn screening results are negative. Unfortunately, most states do not report negative results directly to the pediatrician, particularly if the pediatrician is not the physician of record during the infant’s neonatal stay. All reports are sent to the hospital of birth and not necessarily to the physician, making transfer of such information highly variable from state to state and institution to institution. Some states have developed a direct electronic system whereby these results may be easily obtained by the pediatrician; however, in many instances, a direct and easily accessible system is not currently in place and may require time-consuming efforts on the part of the pediatrician and office staff to obtain a hard copy of the newborn screening results. The Committee on Genetics supports the active involvement of the local academy state chapters in working with state newborn screening programs to facilitate the prompt and direct transfer of information to the pediatrician. Many of these issues are addressed in greater detail in the AAP 1992 policy statement “Issues in Newborn Screening,” which should serve as a reference for these newborn screening fact sheets.

Our knowledge base regarding newborn screening is expanding rapidly, and there are numerous areas of controversy. Recently, the Committee on Assessing Genetic Risks of the Institute of Medicine has recommended that ongoing newborn screening programs be reviewed periodically, preferably by an independent body that is authorized to add, eliminate, or modify existing programs. Furthermore, the committee recommended that states with newborn screening programs for treatable disorders also have programs available to assure that necessary treatment and follow-up services are provided to affected children identified through newborn screening without regard to the ability to pay. Although no clear consensus of the committee was forthcoming regarding informed consent for newborn screening, a strong recommendation was made that informed consent be an integral part of newborn screening, including disclosure of the benefits and risks of the tests and treatments, and that information unrelated to the health of the individual (eg, carrier status and paternity) may be disclosed. For established tests in which patients would clearly benefit from early diagnosis and treatment (eg, phenylketonuria [PKU] and congenital hypothyroidism), it was thought appropriate for state departments of health to mandate the offering of such testing.

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.
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* States as of December 1995. Note: The Uniformed Services Program may contract with any laboratory for the performance of newborn screening. Most hospitals use the newborn screening program in the state in which they are located. Pediatricians should inquire about the newborn screening testing performed on such infants transferring to their practice.

† P indicates selected population, pilot program, or physician request.

Newborn screening varies by state. Information is provided for the following 11 conditions: biotinidase deficiency, branched-chain ketoaciduria (maple syrup urine disease), congenital adrenal hyperplasia (CAH), congenital hypothyroidism, cystic fibrosis (CF), galactosemia, homocystinuria, PKU, sickle cell disease, toxoplasmosis, and tyrosinemia.

These fact sheets will require revision in the future. Your comments and suggestions are appreciated.

ever, was expressed by several committee members that such testing should be universally mandated.

Although we have attempted to provide a consensus viewpoint, experts in this field do not always agree. Pediatricians who desire additional information should contact the specialists in their region or those involved at a national level. General references have been provided to assist in clarifying some of these points.
Note on Cost

Newborn screening entails substantial costs, some of which are inherent in the screening process. All abnormal test results trigger diagnostic and sometimes therapeutic cascades, with their associated economic costs, parental anxiety, and potential for iatrogenic side effects. As more conditions warrant screening for a selected group of treatable devastating disorders costs less than long-term treatment of such disorders costs less than long-term treatment of such conditions. All these costs include the total system’s cost for repeated and confirmatory testing (additional in some states), education, patient and physician notification and contact, follow-up of affected patients, and management (eg, the cost of special dietary supplements) and are not necessarily related to the number of disorders included in the program. Such costs must not be overlooked in the care of identified children.

GENERAL REFERENCES
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Andrews LB. State Laws and Regulations Governing Newborn Screening. Chicago, IL: American Bar Foundation; 1985
Council of Regional Networks for Genetic Services. Early Hospital Discharge: Impact of Newborn Screening. Pass KA, Levy HL, eds. Atlanta, GA: Emory University School of Medicine; 1995
Therrell BL. Advances in neonatal screening. Presented at the Sixth International Neonatal Screening Symposium; November 16-19, 1986, and the Fifth National Neonatal Screening Symposium; November 20, 1986; Austin, TX

Note on Early Hospital Discharge
With collection of specimens for newborn screening when the newborn is younger than 24 hours, concerns have arisen regarding reliability of the assay results in identifying all infants with these disorders. Many newborn screening tests rely on time-dependent changes in the concentration of an analyte in the blood for identification of the congenital condition. These analytes include thyroxine (T₄) and thyrotropin (TSH) for congenital hypothyroidism, phenylalanine for PKU, leucine for maple syrup urine disease, methionine for homocystinuria, galactose for galactosemia, and 17-hydroxyprogesterone (17-OHP) for CAH. The following consensus recommendations of a conference, "Early Hospital Discharge: Impact of Newborn Screening," sponsored by the Maternal and Child Health Bureau, concluded that: (1) the initial newborn screening specimen be collected from all infants as close as possible to the time of discharge from the nursery and in no case later than 7 days of age; (2) if the initial specimen for newborn screening is collected before 24 hours of age, a second specimen should be collected before 2 weeks of age; and (3) all newborns should have primary care providers designated before discharge to ensure prompt and appropriate follow up of newborn screening results. Additional monitoring of the true incidence of false-positive and false-negative test results in samples obtained before 24 hours of age and the development and assessment of technical strategies to increase sensitivity of testing were also recommended. Pediatricians should be aware of current practices in their community and their state with regard to discharge before 24 hours of age, timeliness of obtaining second specimens, and follow-up of such test results.

Andrews LB. Legal Liability and Quality Assurance in Newborn Screening. Chicago, IL: American Bar Foundation; 1995
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BIOTINIDASE DEFICIENCY

State Newborn Screening Availability
Currently available in 19 states, the District of Columbia, and the US Virgin Islands.

Brief Clinical Description
An autosomal recessive disorder of biotin recycling that leads to multiple carboxylase deficiency. Many affected individuals initially show combinations of neurologic and cutaneous findings, including myoclonic seizures, hypotonia, seborrheic or atopic dermatitis, partial or complete alopecia, and conjunctivitis. Other common features include ataxia, hearing loss, optic atrophy, developmental abnormalities, and organic acidemia with acute metabolic decompensation resulting in coma. Death may occur.

Genetics
Chromosomal Map Location. Undetermined.
Incidence. Approximately 1 in 72 000 to 1 in 126 000 in the United States; 1992 Council of Regional Networks for Genetic Services (CORN) data from the newborn screening programs of 17 states yielded 14 confirmed cases in 1 224 018 screened newborns for both profound (<10% activity) and partial (10% to 30%) deficiency (1 in 87 000). Worldwide experience of neonatal screening is 5 in 170 000 in New Zealand, 14 in 195 000 in Quebec, and 6 in 400 000 in West Germany at initial screening. Profound deficiency is 1 in 137 000; partial deficiency is 1 in 110 000 live births worldwide. Estimated heterozygote frequency is 1 in 175.


Racial and Ethnic Variability. Most confirmed cases have been in white patients. The highest incidence has been in French Canadians. Several African-American patients (at least three) and one Hispanic patient have had the condition detected by newborn screening. Japan has identified at least one patient in a very limited screening program.

Molecular Pathology. Biotinidase is a hydrolase that specifically cleaves biotin from biocytin and biotinyl peptides that are formed during the proteolytic turnover of the holocarboxylases (acyetyl-coenzyme A [CoA], β-methylcrotonyl-CoA, propionyl-CoA, and pyruvate carboxylases). It is the primary defect in most individuals with late-onset multiple-carboxylase deficiency.

Potential for Symptomatic Diagnosis. With severe enzyme deficiency, approximately 80% to 85% of patients have metabolic ketoacidosis and organic acidemia. Possibly 15% to 20% of cases will be missed unless a specific quantitative assay for biotinidase activity is requested. Nonspecific features may result in a delayed or missed diagnosis.

Genotype-Phenotype Correlation. Currently being evaluated. Clinical variability exists among affected individuals from different families and also in the expression of this disorder among affected individuals within a sibship. Essentially all the biotinidase-deficient patients who had neurologic symptoms in addition to cutaneous symptoms have had less than 5% activity.

Genetic Counseling. Parents of affected children have serum biotinidase activities intermediate between those of healthy and biotinidase-deficient individuals. A quantitative biotinidase assay is available for carrier detection; the carrier detection accuracy rate is 90% to 95%. Although biotinidase activity can be measured in extracts of amniotic fluid cells, prenatal diagnosis of biotinidase deficiency has not yet been reported. Prenatal treatment may be potentially possible but is probably unnecessary, because heterozygous mothers can supply developing fetuses with adequate amounts of free biotin.

Severity and Variability Without Screening
Mortality. Death has occurred during acute metabolic decompensation, but the frequency is unknown (4 deaths in 20 reported affected). This may be an underreported number, because affected siblings may not have been diagnosed.

Developmental Disabilities. Based on data from 35 patients, the age at onset of neurologic signs and symptoms has varied from 2 weeks to 3 years. Convulsions, ataxia, hypotonia, developmental delay, hearing loss, optic atrophy, and/or decreased vision may occur. Treatment after diagnosis leads to marked improvement, but hearing loss and optic atrophy usually do not resolve. Ultimate psychomotor outcome with postsymptomatic treatment is unknown. The oldest patients at initial presentation were 10 to 12 years.

Physical Findings. Based on 35 patients, the age at onset of symptoms varied from 7 weeks to 3 years. Rash, conjunctivitis, alopecia, and fungal infections may be seen. Symptoms are mild in at least some patients. Some abnormalities are reversible with treatment.

Clinical Outcome With Screening and Treatment
Mortality. None reported (12 cases worldwide).

Clinical Disability. Follow-up has been limited. All positive patients have been asymptomatic after treatment for more than 3 years, with the oldest patient being 8 years of age. No treated infant with partial deficiency has become symptomatic, but little is known about the natural history of partial deficiency. Hypotonia, rash, and acidosis developed in one partially deficient untreated patient with gastroenteritis at 6 months of age; these symptoms then resolved with biotin treatment.
VARIABILITY. Interfamilial and intrafamilial clinical variability is seen. No cases have been identified by screening and have been left untreated to evaluate natural history. No children with 10% to 30% enzyme activity were symptomatic at the time of diagnosis. It is unknown whether completely asymptomatic persons with variant forms exist.

Possible Interventions. Oral biotin has reversed physical and some neurologic findings. Reversal and/or prevention of developmental delay is unclear. Postsymptomatic treatment may not reverse hearing loss and/or optic atrophy and has not improved retardation in some cases. The optimal dosage of biotin is unknown. Hazards of biotin treatment are unknown; treatment with 10 mg/d has been well tolerated to date. Biotin treatment is relatively inexpensive (estimated cost, $25 to $100 per year).

Screening Test Characteristics and Confirmation

Type of Test. Colorimetric assay (for biotinidase) on a dried blood spot. Affected infants and children have 0% to 10% of normal adult activity. Levels between 10% and 30% of mean normal activity levels are considered partial biotinidase deficiency.

Timing. Optimal timing for testing is unknown. Enzyme deficiency has been demonstrated in cord blood; therefore, any specimen obtained after birth is anticipated to be adequate. Symptoms have not developed in most patients before 2 months of age, but one patient was symptomatic at 3 weeks. Thus, rapid turnaround may be needed. The mean age at onset of symptoms is 5 to 6 months.

Stability of Specimen. Samples stored for longer than 18 months at room temperature or higher had nodetectable activity. Activity was detected in samples less than 18 months old. Samples analyzed 1, 30, and 60 days after collection were stable. Specimens are stable frozen at −70°C for 3 years; samples frozen than 18 months at room temperature or higher had no detectable activity.

Accuracy of Screening Test

False-Negative Rate. Unknown. Rare (<1%) false-negative test results may occur with the use of sulfonamides. All samples tested after the newborn period should be checked for the presence of sulfonamides.

False-Positive Rate. Unknown.

Ongoing Studies. A pilot screening program was initiated at the Medical College of Virginia by Barry Wolf. Screening is also being conducted in 15 countries worldwide. Follow-up of screening cases is in progress. Information is needed concerning incidence, natural history, efficacy of treatment (including evaluation of older, previously asymptomatic patients), parameters for optimal treatment, and heterogeneity of the disorder.

Special Concerns and Issues

Postsymptomatic treatment may be as effective as presymptomatic treatment in some cases. The risks of treatment are unknown, but no complications have been reported to date. The oldest known patient is 18 years; therefore, the long-term outcome of treatment is unclear. Some biotin preparations available at pharmacies or health food stores may not provide adequate doses of biotin.

Professional and Public Education

Biotinidase deficiency is a recently described metabolic disorder with limited professional and public awareness. Educational efforts are needed.

GENERAL REFERENCES


BRANCHED-CHAIN KETOACIDURIA: MAPLE SYRUP URINE DISEASE

State Newborn Screening Availability

Currently part of newborn screening in 23 states, the District of Columbia, and the US Virgin Islands.

Brief Clinical Description

An autosomal recessive disorder of branched-chain ketoacid decarboxylation resulting in high body fluid (serum, urine, and spinal fluid) levels of
leucine, isoleucine, valine, and their corresponding ketoacids. Lethargy, irritability, and vomiting progressing to coma and death occur in affected individuals if untreated.

Genetics

Chromosomal Map Location. 19q13.1–q13.2 (branched-chain ketoacid dehydrogenase).

Incidence. US mixed population, 1 in 250,000 to 1 in 400,000; New England Newborn Screening Program, 1 in 290,000; Supplemental Newborn Screening Program in Pennsylvania, 1 in 170,000 to 1 in 175,000; 1992 CORN data, 1 in 209,000 (6 confirmed cases in 1,256,605 screened newborns); and 1 in 180,000 in Quebec.


Racial and Ethnic Variability. Highest in Mennonite population (1 in 760). May be more common in African-American and Asian populations.

Molecular Pathology. Branched-chain ketoacid dehydrogenase deficiency. Branched-chain ketoacid disease complex consists of four proteins: E1, two proteins (binding sites for thiamine phosphate and ketoacid substrate); E2, which transfers acyl groups to CoA; and E3, flavoprotein lipomide. Specific point mutations and base deletions in the genes for these proteins in the enzyme complex have been defined and correlate with affected status.

Potential for Symptomatic Diagnosis. High and should be considered in any infant with severe acidosis in the first 10 days of life. Initial symptoms are poor feeding and marked lethargy. The odor of the urine is characteristic. Elevated levels of urine and plasma branched-chain amino acids and ketoacids are found; plasma leucine levels are extremely elevated (1000 to 5000 μmol/L in classic form and 50 to 4000 μmol/L in other variants). Levels of urine branched-chain ketoacids are elevated during illness. Confirmation is obtained by plasma leucine levels, quantitative urine branched-chain ketoacids, and measurement of leucine-decarboxylating activity in white cells.

Genotype-Phenotype Correlation. Several different allelic variants have been described, which vary in severity, age at onset, clinical symptoms, and thiamine responsiveness. The classic form presents with severe early onset, constant branched-chain amino acid excretion and 0% to 2% of normal substrate oxidation. Early neonatal symptoms include poor feeding, seizures, coma, and ketoacidosis. An intermittent form is triggered by protein stress (high protein intake) with intermittent branched-chain amino acid excretion and 2% to 40% of normal substrate oxidation. The intermediate form is associated with mental retardation and ataxia but no ketoacidosis, mild constant urinary branched-chain amino acid excretion, and 5% to 25% of normal substrate oxidation. The thiamine-responsive form is usually milder, of later onset, and characterized by recurrent ataxia and occasional developmental delay. Such patients show constant branched-chain amino acid excretion, no ketoacidosis, and about 40% of normal substrate oxidation.

Genetic Counseling. Carriers show no detectable elevations in branched-chain amino acids or ketoacids under most circumstances. They can be distinguished biochemically using cultured skin fibroblasts to assess branched-chain ketoacid dehydrogenase activity or branched-chain amino acid oxidation. Heterozygotes usually show 50% activity compared with control cells. Prenatal diagnosis is available using cultured amniotic fluid or chorionic villus cells.

Severity and Variability Without Screening

Mortality. Lethal in classical form, usually in the first month of life, if unrecognized and untreated.

Developmental Disabilities. Symptomatic patients frequently have irreversible retardation.

Physical Findings. Spastic quadriparees, dystonic posturing, dysarthria, and poor physical growth are common.

Clinical Outcome With Screening and Treatment

Mortality. All deaths cannot be prevented. At least one infant died at 9 days of age, 1 day before newborn screening results were reported. Death within the first 2 weeks is not uncommon, and about one third of the infants have died before dietary therapy could be instituted. Some patients die suddenly at older ages despite therapy.

Clinical Disability. Age and neurologic symptoms at the time therapy is instituted affect outcome. Treated patients frequently have irreversible retardation. Although about 27% of more recently reported treated patients have IQs higher than 90, the outcome is related to the time between the onset of symptoms and therapy. Best outcomes have been achieved in second affected newborns in identified families and when treatment is begun within 24 hours of symptoms.

Variability. The outcomes of treated patients are only available for the classic form. Additional data are needed to evaluate the outcome of genetic variants detected by newborn screening programs.

Possible Interventions. Screening programs require immediate retrieval, diagnosis, and treatment of affected infants. Dietary restriction of branched-chain amino acids requires frequent monitoring that must be continued indefinitely. Commercial formula is available, but intake of branched-chain amino acids must be individually titrated. A nutritionist and specially trained physician must coordinate therapy. The cost is variable and based on long-term use of the special formula.

Screening Test Characteristics and Confirmation

Type of Test. Bacterial inhibition assay (BIA) for leucine using a dried blood spot.

Timing. Because symptoms occur early, results must be available in less than 2 weeks, and the specimen must be obtained as early as possible. Af-
ected infants have had elevated leucine levels by 4 to 14 hours of age regardless of protein intake. The presence of alloisovaline has been detected as early as 14 hours of age. Leucine screening may not be sensitive if obtained before 12 hours of age.

**Stability of Specimen.** Short-term stability is excellent; longer-term stability is presumed excellent at −70°C, but limited information is available under special or ambient conditions.

**Confirmation.** Quantitative measurement of leucine, isoleucine, and valine; presence of alloisoleucine in serum; and elevated levels of urine branched-chain amino acid and ketoacids. Specific enzymatic assays are available in research laboratories.

**Ac~curacy of Screening Test**

**False-Negative Rates.** Extremely low, greater than 99.9% specificity. May be dependent on age at testing.

**False-Positive Rates.** Limited information.

**Ongoing Studies.** Programs continue to evaluate the effectiveness of screening and dietary management. Additional information is needed concerning ethnic variation in the incidence of classic and variant forms, long-term prognosis, management at different ages, possibilities for improving turnaround times, and efficacy of screening at different ages (ie, 24 hours as opposed to later).

**Special Concerns and Issues**

Infants often have irreversible damage by the time they are identified by newborn screening programs. Therefore, a rapid turnaround time and screening program coordination are necessary. Specialized care, including nutritional assessment and planning, the ability to monitor amino acids, and long-term assessment, is necessary to achieve the best potential outcomes.

**Professional and Public Education**

Awareness of this disorder is limited. Aggressive education of physicians with emphasis on early clinical suspicion, even in states with newborn screening programs, remains paramount because of the sudden early onset of this disorder with poor outcomes when dietary intervention is begun later than 24 hours after the onset of symptoms.

**GENERAL REFERENCES**


**CONGENITAL ADRENAL HYPERPLASIA**

**State Newborn Screening Availability**

Currently performed in 11 states.

**Brief Clinical Description**

CAH consists of a family of disorders arising from specific defects in the enzymes of the adrenal cortex required for the biosynthesis of adrenal corticosteroids. The most common form results from 21-hydroxylase deficiency, which accounts for more than 90% of all recognized cases. This form can be detected by neonatal screening and is the only condition discussed in this section. The detect results in increased androgen production, which is responsible for the somatic and sexual precocity seen in these patients. In the female newborn, the fetal adrenal androgens may masculinize the external genitalia to the extent that an incorrect male sex assignment is made. In approximately 75% of affected newborn boys, a “salt-losing syndrome” may be the only clinical finding leading to the correct diagnosis. Treatment suppresses the abnormal steroid pattern and avoids the consequences of excess virilization, short stature, and cortisol deficiency.

**Genetics**

**Chromosomal Map Location.** 21-Hydroxylase: 6p22. Closely linked to the HLA major histocompatibility complex.

**Incidence.** One in 12,000. The 1992 CORN data yielded 51 confirmed cases of classic CAH (salt-wasting and simple virilizing) in 1224,018 screened newborns (1 in 20,000).

**Inheritance.** Autosomal recessive. In clinically detected cases, girls exceed boys because of masculinization of the female fetus and neonatal death in undetected salt-wasting boys.

**Racial and Ethnic Variability.** White, 1 in 12,880; Japanese, 1 in 15,000; Yupik Eskimo, 1 in 680; and Italian, 1 in 5500 to 1 in 10,000.

**Molecular Pathology.** The clinical consequences of 21-hydroxylase deficiency arise primarily from the overproduction and accumulation of precursors proximal to the blocked enzymatic step. These are shunted into the androgen biosynthetic pathway.
The 21-hydroxylase functional gene (CYP21B) is closely linked to the HLA major histocompatibility complex, specifically adjacent to the C4B gene encoding the fourth component of serum complement. This cluster is located between the HLA-B and -DR regions on the short arm of chromosome 6. About 25% of classic deficiency alleles are deletions of CYP21B; many of the remaining mutant alleles result from deleterious mutations in the adjacent pseudogene, which then encodes a defective protein, a phenomenon termed gene conversion.

Potential for Symptomatic Diagnosis. Generally good (some cases may be missed) for affected girls with classic 21-hydroxylase deficiency who are born with ambiguous genitalia due to prenatal exposure to elevated levels of androgens. Postnatally, both sexes manifest rapid somatic growth, with accelerated skeletal maturation, early closure of the epiphyses, and short adult stature—a problem that may not be completely prevented by current therapy. Of major concern are those newborns who also have a defect in their ability to synthesize aldosterone and may die in the newborn period from shock caused by salt wasting. Diagnosis is confirmed by the presence of elevated plasma levels of 17-OHP.

Genotype-Phenotype Correlation. There seem to be specific associations between HLAs (ie, haplotypes) and different forms of 21-hydroxylase deficiency. Haplotypes HLA-A3, -Bw47, -DR7, and -Bw60 are associated with salt wasting; HLA-B5 is associated with simple virilizing disease; and HLA-B14 and -DR1 are associated with the nonclassic disease. HLA-A1, -B8, and -DR3 haplotypes are negatively associated with 21-hydroxylase deficiency.

Genetic Counseling. Autosomal recessive, with 25% risk for siblings. Prenatal diagnosis is possible with DNA linkage and/or direct analysis for identification of 21-hydroxylase mutations by chorionic villus sampling in the first trimester and hormonal measurement, HLA polymorphism, and additional specific DNA studies by amniocentesis in the second trimester. HLA typing and DNA studies may allow detection of carriers in families with affected children.

Severity and Variability Without Screening

Mortality. Life-threatening adrenal crises in the newborn period (mortality, 9%).

Developmental Disabilities. Usually absent but may occur from salt-losing crisis and shock.

Physical Findings. Masculinization of female genitalia may be present at birth and may result in incorrect sex assignment. In severe forms, adrenocortical insufficiency, salt-losing crises, and ambiguous genitalia are seen in female patients. Those infants with partial forms have adequate but limited synthesis of cortisol and aldosterone. Such patients are able to respond appropriately to all but severe stress. Virilization and ambiguous genitalia occur in girls; early postnatal virilization occurs in boys. Adult sexual dysfunction has been reported. Increased androgenic secretion also causes accelerated early growth with premature fusion of epiphyses and ultimate short stature.

Clinical Outcome With Screening and Treatment

Mortality. Reduced substantially, but the frequency is unknown because of early onset, salt-losing crises that may occur before the screening results are available. A number of patients have been in severe crises at the time newborn screening results became available.

Clinical Disability. Should be reduced because of early treatment.

Variability. Early diagnosis should lead to correct sex identification, eliminate problems of precocious puberty, masculinization, and accelerated growth; and decrease fertility problems in affected girls. The risk of adrenal crisis with stress is still present.

Possible Interventions. Endocrinologic consultation is recommended. Treatment with glucocorticosteroids serves the dual purpose of replacing cortisol and suppressing excessive corticotropin production. Patients with loss of salt and elevated plasma renin activity should receive mineralocorticoid therapy and may need supplemental salt intake in addition to hydrocortisone. The dose of glucocorticosteroids should be appropriately increased for stress or illness. Resection of the enlarged clitoris should be done as soon as feasible, with additional surgery (vaginoplasty) performed at puberty.

Screening Test Characteristics and Confirmation

Type of Test. Enzyme immunoassay or radioimmunoassay for measurement of 17-OHP in 21-hydroxylase deficiency can be performed on dried blood spots.

Timing. Elevation of 17-OHP is present at birth, although levels obtained before 24 hours of age may be physiologically high. Rapid turnaround time may be needed to detect boys and those nonvirilized undetected girls who may present with early onset adrenal crises and salt losing. Premature infants may have false-positive test results. Screening in the first 48 hours may increase the false-positive rate, but further study is needed. Screening at 1 to 2 weeks of age detects some additional cases of simple virilizing CAH and increased numbers of the nonclassic form of 21-hydroxylase deficiency.

Stability of Specimen. No decomposition of 17-OHP has occurred after periods of as long as 30 days in blood dried on filter paper stored at room temperature.

Confirmation. Quantitative measurement of plasma 17-OHP, available from many commercial laboratories. A relatively small sample of blood is required.

Accuracy of Screening Test

False-Negative Rate. Low: detects most cases (95%) of 21-hydroxylase deficiency. With an initial screen of more than 65 ng/mL, 3% of salt wasters may be missed if screened before 24 hours of age.

False-Positive Rate. Ranges from 0.2% to 0.5%, depending on the cutoff level chosen. The cross-react-
tion of steroid compounds related to 17-OHP depends on the antisem used in the immunoassays of steroids and whether organic solvent extraction is included in the testing protocol.

**Ongoing Studies.** Pilot screening programs have been completed in Alaska and Washington and in several countries (Japan, Italy, France, Scotland, Sweden, and New Zealand). Further data are needed to assess false-negative and false-positive rates and to determine the extent to which clinical outcome is improved by early diagnosis and treatment.

**Special Issues and Concerns**

Analagous of hydrocortisone or cortisone are effective at suppressing adrenal androgens, but a dose of any glucocorticoid that is too high may result in growth suppression.

**Professional and Public Education**

Limited general knowledge. Simple, inexpensive screening is available, but this is not well known. Education of health professionals regarding CAH in testing female newborns with ambiguous genitalia is of paramount importance in all populations. Without screening, diagnosis is difficult in male newborns unless they become symptomatic.

**GENERAL REFERENCES**


Gonzalez J. Congenital adrenal hyperplasia. Presented at the conference on Early Hospital Discharge: Impact on Newborn Screening; March 31, 1995; Washington, DC


**CONGENITAL HYPOTHYROIDISM**

**State Newborn Screening Availability**

Performed in all 50 states, the District of Columbia, Puerto Rico, and the US Virgin Islands.

**Brief Clinical Description**

Results from an inadequate production of thyroid hormone, which may be due to a number of factors: agenesis or ectopic thyroid gland, genetic disorders of thyroid hormonogenesis, endemic cretinism, and hypopituitarism. Patients who are not identified and treated promptly have mental retardation and variable degrees of growth failure, deafness, and neurologic abnormalities, as well as classic hypometabolic symptoms of hypothyroidism.

**Genetics**

**Chromosomal Map Location.** Has multiple causes, most of which are nongenetic.

**Incidence.** One in 3600 to 1 in 5000 in the United States from screening; 1 in 3000 in Europe; 1 in 6600 to 1 in 7300 in Sweden by clinical diagnosis; and 1 in 5700 in Japan.

**Inheritance.** Usually sporadic. Disorders of thyroid hormonogenesis may be inherited as autosomal recessive traits. Thyroid hormone transport defects may be X linked. Sex ratio: 3:1, female to male (New England states), 2:1 female to male by clinical diagnosis.

**Racial and Ethnic Variability.** Considerably less in African-American populations (1 in 17 000 in Georgia and 1 in 10 000 in Texas); more prevalent in Hispanic populations (1 in 2700) and Native Americans (1 in 700).

**Molecular Pathology.** The fetal hypothalamic-pituitary-thyroid axis begins to function by midgestation and is mature in the full-term infant. If fetal hypothyroidism develops, untoward effects may be demonstrated in the central nervous system and skeleton. However, most infants with congenital hypothyroidism appear normal at birth. The hypothyroid fetus is partially protected by placental transfer of maternal thyroid hormone; T3 levels in cord blood of athyroid fetuses approximate one third of maternal levels.

**Potential for Symptomatic Diagnosis.** Clinical signs of hypothyroidism (other than neonatal jaundice) may not appear until the infant is several months of age or older. Infants with early clinical findings seem to have a higher incidence of developmental disabilities. The observation of a higher incidence from screening programs than from clinical surveillance suggests that cases may be missed.

**Genotype-Phenotype Correlation.** Embryogenic defects of the thyroid gland can lead to ectopy (50% to 55%) or aplasia or hypoplasia (30% to 35%), accounting for 85% of the cases of congenital hypothyroidism. Inborn errors of metabolism of thyroid hormonogenesis account for 10% to 15%, which are termed primary hypothyroidism. Embryogenic defects or inborn errors at the level of the pituitary or hypothalamus (secondary and tertiary hypothyroidism) represent less than 4% of cases.
Genetic Counseling. Depends on the diagnosis or cause of the hypothyroidism. Dyshormonogenesis occurs most commonly as a result of autosomal recessive genetic conditions and may occur in siblings. Other causes may have a familial basis. Determination of cause may require other hormonal studies, evaluation for other congenital defects (occurs in 10% of these infants), and radionucleotide scanning of the thyroid gland.

Severity and Variability Without Screening

Mortality. May be underestimated because of failure of diagnosis. The historical increase in mortality in retarded patients may be related to institutionalization.

Developmental Disabilities. Vary in different studies. On the basis of approximately 800 untreated patients in the literature, the mean IQ was 80. Of 250 patients with reported test results, 67% had IQs of less than 85, 40% had IQs of less than 70, and more than 19% had IQs of less than 55. Other neuropsychologic problems are common. The degree of developmental disability is probably different for different types of hypothyroidism.

Physical Findings. May include poor growth, goiter, low metabolic rate, constipation, poor peripheral circulation, bradycardia, and myxedema. More than 95% of infants with sporadic hypothyroidism show such minimal signs at birth that the diagnosis is missed.

Clinical Outcome With Screening and Treatment

Mortality. Not expected.

Clinical Disability. Contradictory results from large studies. The New England Congenital Hypothyroidism Collaborative study showed normal IQ, visual motor integration, and neuropsychologic profiles when compared with control values. The Quebec study showed normal developmental quotients, but the scores were significantly lower than control values. No growth or physical abnormalities were noted with treatment. The Ontario study also showed intelligence within the normal range, but the children had cognitive and neuromuscular impairment that seemed to reflect the severity and time of onset of thyroid hormone deficiency. Recent studies from England and the Netherlands using screening T₄ levels less than 50 μmol/L were predictive of a decline in IQ.

Variability. The New England Congenital Hypothyroidism Collaborative showed that the only correlation with outcome and disease-related factors is adequacy of treatment and compliance. Other studies indicated that low thyroid hormone levels, agenesis, and evidence of fetal hypothyroidism are associated with poor outcome in some cognitive areas. Attention deficit problems have been observed in older children with elevated circulating levels of T₄ due to thyroid hormone receptor defects. Treatment should be undertaken within the first few weeks of life to prevent permanent retardation of intellectual function and/or skeletal growth.

Possible Intervention. Oral levothyroxine should be given at a dosage to produce a T₄ concentration in the upper half of the normal range by 2 weeks after the initiation of therapy. Growth and development must be monitored at monthly intervals, including frequent laboratory evaluations of thyroid hormone levels to prevent poor achievement associated with low levels (eg, inadequate dosage and noncompliance) and behavior problems associated with high levels. Consultation with a pediatric endocrinologist is advisable.

Screening Test Characteristics and Confirmation

Type of Test. Radioimmunoassay for T₄, TSH, or both. North American programs generally screen using T₄ values followed by TSH levels on the lowest 5% to 10%. The use of primary TSH screening is routine in Europe and Japan. Simultaneous determination of both T₄ and TSH is optimal. Nonisotopic enzyme immunoassays have been developed for both TSH and T₄. The use of simultaneous enzyme immunoassay methods should allow less expensive T₄ and TSH testing. Each type of test has been adapted for use with dried filter paper blood spots. The T₄-screening approach can also identify infants with T₃-binding globulin deficiency (1 in 5000 to 1 in 10 000) or hypothalamic-pituitary hypothyroidism 1 in 50 000).

Timing. Newborns older than 12 hours for T₄ testing. Specimens collected in the first 24 to 48 hours of life may lead to false-positive TSH elevations using any screening test approach. Retesting of a second sample for T₄ has led to identification of an additional 6% to 12% of cases.

Stability of Specimen. Stable for many months if refrigerated with a desiccant.

Confirmation. Quantitative measurement of T₄ and TSH; the free T₄ value is low, and the TSH level is elevated. A response to TSH-releasing hormone is occasionally needed to investigate secondary or tertiary hypothyroidism. Radioisotope scanning is necessary to identify the cause of the hypothyroidism. Repeated testing may be necessary to identify transient hypothyroidism.

Accuracy of Screening Test

False-Negative Rate. Depends on the cutoff used, the screening methods, and the age of the infant. Approximately 10% of cases are detected only by a second screening at 2 to 6 weeks of age. True biological false-negative test results account for about 11% of missed cases. Primary TSH screening misses secondary or tertiary hypothyroidism.

False-Positive Rate. Depends on the tests and cutoffs used. T₄ testing alone has low specificity, with a false-positive rate as high as 0.3%. T₄ testing followed by testing for TSH and, when indicated, T₃-binding globulin, reverse triiodothyronine, or free T₄ produces high specificity. Recall rates vary from 0.04% to 0.5%.

Ongoing Studies. Studies include long-term outcome, correlation of severe disease with possible prenatal effects, incidence of transient disease, hypothy-
roidism in premature infants, optimal diagnostic studies, and clinical management protocols.

Special Concerns and Issues

Normal newborn thyroid test results may decrease vigilance for clinically symptomatic patients. The most common neonatal signs are prolonged jaundice, constipation, and umbilical hernia. Prevention of overtreatment requires careful follow-up evaluations, including thyroid function tests, to minimize the risks of increased intracranial pressure and/or craniosynostosis. A subgroup of premature infants exists in which the infants are at increased risk of true transient hypothyroidism as well as low T4 levels with euthyroidism and low T3-binding globulin levels.

Professional and Public Education

Generally adequate. Brochures for parents are provided by state newborn screening programs and are available before or after delivery. Educational information also is provided with positive screening test results. Routine mandated screening may lead to a less efficient diagnosis of missed symptomatic infants, because the clinician may assume that the disorder has been definitively ruled out.

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Holtzman C, Slayzey WE, Cordero JF, Hannon WH. Descriptive epidemiology of missed cases of phenylketonuria and congenital hypothyroidism. Pediatrics. 1986;78:553–558


CYSTIC FIBROSIS

State Newborn Screening Availability

Currently available in two states with pilot or voluntary programs in two additional states.

Brief Clinical Description

An autosomal recessive disorder characterized by a generalized disturbance in exocrine function related to an abnormal transmembrane regulator protein that has properties of a chloride channel.

Genetics

Chromosomal Map Location. Long arm of chromosome 7: q31.

Incidence. Northern European, 1 in 2000 average (heterozygote, 1 in 22); African-American, 1 in 17 000 (heterozygote, 1 in 65); Hispanic, 1 in 9000 (heterozygote, 1 in 45).


Racial and Ethnic Variability. Seventy percent of the mutations found in northern Europeans have a ΔF508 (phenylalanine) deletion. Current surveys indicate that 85% to 90% of CF carriers in the North American white population can be detected by testing for 12 to 32 mutations; the carrier detection rate is greater than 95% in Ashkenazi Jews but substantially less in African-Americans, Hispanics, and Asians.

Molecular Pathology. Defective CF transmembrane regulator protein results in thick mucus secretions, chronic obstructive lung disease, recurrent pulmonary infection, cor pulmonale, and death. In the majority of cases, exocrine pancreatic dysfunction begins in utero and may cause meconium ileus at birth, postnatal steatorrhea, and failure to thrive. Other manifestations include abnormally high levels of sweat sodium and chloride, cirrhosis of the liver, abnormal glucose tolerance, absence of the vas deferens, and infertility in boys.
Potential for Symptomatic Diagnosis. Good with meconium ileus, which occurs in about 10% of affected newborns. It is generally good for a patient with malnutrition and recurrent pulmonary problems, but considerable delay frequently occurs. At least half of patients with CF go undiagnosed during the first year of life; 25% remain undiagnosed by the end of the second year.

Genotype-Phenotype Correlation. Several hundred different mutations have been identified. The most common ΔF508 homozygous deletion results in pancreatic insufficiency and severe disease in 99% of patients, whereas only 36% of patients with CF have other mutations have pancreatic insufficiency. Milder disease states and pancreatic sufficiency occur with other less common mutations and compound heterozygotes (eg, two different mutations at the CF locus). The genotype-phenotype relationship, however, is not simple, because there is more phenotypic variation within the ΔF508 population than there is among groups with different mutations.

Genetic Counseling. Prenatal diagnosis is possible for most families, particularly with available probands. Carrier screening of the general population is possible using available DNA mutation analysis, which currently detects 80% to 90% of the heterozygote population, depending on the ethnic background. It is difficult to detect all carriers. Although the feasibility of carrier-screening programs is currently being evaluated, CF carrier testing is not recommended at this time for most individuals or couples who do not have family histories of CF. The primary benefit of newborn screening lies in the potential prevention of malnutrition as well as possible improved pulmonary status and avoidance of protracted medical evaluations; this benefit has not been noted in some studies. Families of affected individuals should be counseled regarding carrier detection for other family members. Gene therapy is currently under investigation.

Severity and Variability Without Screening

Mortality. Ten percent of neonates with CF have small-bowel obstruction due to meconium ileus, which may lead to death in some cases. Neonates and infants have 13% mortality from malabsorption and malnutrition. In the second to fourth decades of life, death results from obstructive pulmonary disease and infection. Mean survival is now in the mid to late 20s.

Developmental Disabilities. Rare; normal intelligence.

Physical Findings. Poor growth with chronic respiratory infections, malabsorption, and gastrointestinal abnormalities.

Clinical Outcome With Screening and Treatment

Mortality. Conflicting study results have been reported with early intervention, but reduced morbidity and mortality from malnutrition in infancy has been suggested (Colorado study). No difference in height and weight was noted by 4 years of age in a study from Wales. Significant differences in survival and clinical outcome among screened and nonscreened infants with CF have been reported from Italian, Dutch, and Australian studies.

Clinical Disability. The impact of newborn screening remains unknown. Early initiation of appropriate treatment may reduce nutritional and pulmonary disability.

Variability. There is no characteristic pattern regarding the severity of the disease, which may vary depending on the specific mutations involved, as well as other epigenetic factors. Different homozygote family members can have mild or severe disease, with a wide spectrum in the natural history of this disorder.

Possible Interventions. Improved parenteral and oral nutrition, fat-soluble vitamin supplements, predigested formula, and pancreatic enzyme replacement enable more normal growth. Improved patient outcome also has been seen with pulmonary treatment with bronchodilator therapy, bronchial drainage with chest physiotherapy, and major advances in anti-Pseudomonas drugs and synergistic combinations of aminoglycoside, semisynthetic penicillin derivatives and aerosolized antibiotics. Newer aerosolized DNase, amiloride, adenosine triphosphate, uridine triphosphate (an extracellular nucleotide that augments chloride secretion by CF respiratory epithelial cells), and a Pseudomonas vaccine are currently being evaluated. Gene therapy using recombinant DNA in an appropriate viral vector is under investigation and evaluation.

Screening Test Characteristics and Confirmation

Type of Test. The immunoreactive trypsin (IRT) test of dried blood spots, which uses an immunoassay, is the screening test in the neonatal period. The sharp decline in plasma concentration during the first 6 months of life decreases further in older children. Normal values are 70 to 140 μg/mL, depending on the test kit and antibody used.

Timing. Neonatal period; although elevations of IRT decline after the first several months of life, timing is not critical. IRT assays are of little or no value in older infants and children.

Stability of Specimen. Long-term stability and optimal storage conditions have not yet been reported.

Confirmation. The optimal approach is currently under investigation. The Colorado program uses serial IRT testing of those infants having a value of greater than 140 μg/mL with a second dried blood specimen at about 30 days of age. Persistent elevation of greater than 80 μg/mL requires confirmation by a sweat test and/or DNA analysis. The Wisconsin pilot program performs ΔF508 DNA analysis on the same filter paper for all specimens greater than the initial cutoff value, thereby permitting confirmation if the specimen is homozygous for ΔF508.

Accuracy of Screening Test

False-Negative Rate. Three percent to 5%; an increase in false-negative test results as great as 11.5% occurs among infants with meconium ileus. The IRT test detects 95% of infants with CF who do not have
meconium ileus. Mutations that allow for pancreatic sufficiency may also be missed by IRT screening, because the IRT level will be normal.

False-Positive Rate. Elevated IRT in the neonatal period should have a high degree of specificity, because pancreatitis is extremely rare in the newborn. The false-positive–true-positive ratio with an initial cutoff of greater than 140 µg/mL was 12:1. Incorporating δF508 analysis in the presence of an elevated IRT analysis as part of the initial screening program adds to the specificity of screening.

Ongoing Studies. More than 4 million newborn infants have been screened worldwide. Wisconsin and several commercial newborn screening laboratories are using a two-step approach involving an initial IRT with δF508 analysis on the same (or subsequent) specimen for confirmation. Extensive research is needed to determine the value of early treatment, genotype-phenotype correlations for predicting disease severity, reliability and validity of screening methods, and benefits and/or risks of early detection, including stress on the family because of large numbers of false-positive test results.

Special Concerns and Issues
The impact of a presymptomatic diagnosis on the child and in reproductive planning for the family is unknown. The value of the IRT test in reducing the number of missed cases of CF is under investigation. Research will be enhanced by the potential identification of a large population of presymptomatic patients. There is concern that children and their families with false-positive IRT test results may be psychologically harmed. Physicians may dismiss consideration of CF based on normal screening results and then may not respond appropriately to symptomatic patients.

Professional and Public Education
Although CF has wide public awareness, the potential for newborn screening has not been widely recognized. This may increase with the availability of newer treatment modalities, including gene therapy.

GENERAL REFERENCES

GALACTOSEMIA
State Newborn Screening Availability
Currently available in 44 states, the District of Columbia, and the US Virgin Islands.

Brief Clinical Description
An inherited disorder of galactose metabolism leading to failure to thrive, vomiting, liver disease, cataracts, and mental retardation in untreated survivors; lethal in most cases.

Genetics
Incidence. One in 60,000 to 1 in 80,000; 1992 CORN data, 1 in 70,000 for classic galactosemia and 1 in 16,000 for other variant forms of galactosemia.


Racial and Ethnic Variability. None reported.

Molecular Pathology. The genetic disturbance is expressed as a cellular deficiency of GALT (the defect in the severe form of galactosemia), galactokinase, or uridine diphosphate-galactose-4-epimerase—the enzymes catalyzing the reactions in the unique pathway by which galactose is converted to glucose. Only newborn screening for GALT deficiency will be addressed in this section. Many missense mutations in highly conserved regions of the GALT gene have been identified, the most common being missense mutation Q188R, present in 90% of the Irish homozygous G/G population. This mutation is found in about 50% of the African-American alleles. Genetic compounds and variants with less severe clinical symptoms and higher enzyme activity have been described.

Potential for Symptomatic Diagnosis. Fair. Symptoms may occur before receiving the results of newborn screening and require a high index of suspicion. In one survey, two thirds of the infants were symptomatic and under care at the time of the report of the positive newborn screening result. Simple urine screening shows non-glucose-reducing substances (galactose). A galactose-free diet and supportive care for Escherichia coli sepsis, hypoglycemia, liver failure, and coagulation problems should be instituted pending confirmation of the diagnosis.

Genotype-Phenotype Correlation. Genotype-phenotype correlations are emerging with relation to the specific gene mutation and enzyme level. In a subset of African-American patients, despite the absence of GALT activity in red cells, 10% enzyme activity is present in the liver and intestine with milder disease. The Duarte variant has 50% erythrocyte transferase activity and a faster starch gel electrophoretic pattern. A variety of other clinical variants show differing but measurable levels of red cell transferase activity and are characterized by their altered electrophoretic mobility.

Genetic Counseling. All enzymatic defects are inherited as autosomal recessive conditions. Prenatal diagnosis is possible.

Severity and Variability Without Screening

Mortality. Usually fatal. In classic galactosemia, symptoms occur within the first 2 weeks of life; jaundice, vomiting, lethargy, hepatosplenomegaly, cataracts, and failure to thrive may proceed to death and severe morbidity from liver failure, sepsis, or bleeding if untreated. E.coli sepsis may be a presenting sign.

Developmental Disabilities. Present in survivors.

Physical Findings. Cerebral palsy, ataxia, seizures, mental retardation, cataracts, and liver disease.

Clinical Outcome With Screening and Treatment

Mortality. None expected, but some infants may die before the results of the screening test are available because of susceptibility to E.coli sepsis.

Clinical Disability. The mean IQ is in the low end of the normal range, but the range is wide. The IQ seems to be dependent on the time of treatment, with best results (normal IQ) obtained when treatment is started before 10 days of age. Visual-perceptual, speech, and other learning disabilities are common. Ovarian failure with hypergonadotropic hypogonadism and primary or secondary amenorrhea has occurred in the majority of treated females.

Variability. Phenotype classification using red cell enzyme assays and electrophoretic mobility is necessary to determine treatment and compare outcomes.

Possible Interventions. A galactose-free diet should begin as soon as possible and should continue throughout life. Galactose, a product of lactose metabolism, is the compound that cannot be metabolized. Avoidance of lactose and lactose-containing products is essential. Galactose-1-phosphate levels are sometimes used to determine compliance. Evaluation for learning disabilities should be performed as needed, and appropriate intervention should be arranged.

Screening Test Characteristics and Confirmation

Type of Test. Test for elevated blood galactose content: microbiologic test using E.coli or E.coli in combination with a bacteriophage (Paigen test). Test for deficient GALT enzyme activity: fluorescent spot-screening test (Beutler test). Most newborn screening laboratories use a combination of the Beutler test and a fluorometric assay for galactose (Hill test). In the latter test, the assay conditions are adjusted so that fluorescence is visible only when total galactose is increased, usually more than 8 to 10 mg/dL.

Timing. Screening by measurement of enzyme GALT is accurate at any time. Methods measuring galactose accumulation require ingestion of milk. Patients who have had transfusions may have negative Beutler test findings for as long as 2 to 3 months. Rapid screening is necessary because of E.coli sepsis and presence of neurologic residua in patients treated late.

Stability of Specimen. Satisfactory for screening, but the stability of transferase decreases in hot, humid climates, and false-positive results become common.

Confirmation. Quantitative measurement for galactose, galactose-1-phosphate, and starch gel electrophoresis for transferase enzyme. Family studies may be necessary to determine the genotype.

Accuracy of Screening Test

False-Negative Rate. Excellent for homozygous classic transferase deficiency, but partial deficiencies (especially Duarte or Duarte/galactosemic compound heterozygotes) may be missed.

False-Positive Rate. Varies with test; false-positive results are especially high during hot summer months with the Beutler test.
Ongoing Studies. Ovarian failure in affected females, speech problems and learning disabilities in treated patients, rigidity of diet restrictions, and clinical manifestations of compound heterozygotes and other variants are currently being studied.

Special Concerns and Issues

Rapid turnaround time is needed because of early onset of symptoms; physician awareness of this disorder needs to be maintained. Follow-up care requires specialized metabolic and genetic clinics providing nutritional, psychologic, nursing, biochemical, and pediatric care. There is a need for further information concerning the clinical manifestations in genetic variants and the incidence of catacacts and gonadal failure among carriers.

Professional and Public Education

The public is generally unaware of this disorder. Information is provided during the neonatal period in the form of brochures developed by state newborn screening programs.

GENERAL REFERENCES


HOMOCYSTINURIA

State Newborn Screening Availability

Currently performed in 20 states, the District of Columbia, and the US Virgin Islands.

Brief Clinical Description

An autosomal recessive defect in the catabolism of sulfur-containing amino acids. The most common cause of homocystinuria is a deficiency of the enzyme cystathionine β-synthase. Elevated levels of homocysteine, methionine, and metabolites of homocysteine accumulate in the blood and urine of these patients. Clinical problems include thrombembolism, optic lens dislocation, scoliosis, osteoporosis, developmental and mental retardation, seizures, psychiatric disturbances, myopathy, and a marfanoid habitus.

Genetics

Chromosomal Map Location. Long arm of chromosome 21: 21q22.

Incidence. One in 50,000 to 1 in 150,000; 1992 CORN data, 1 in 670,000, with only 2 confirmed cases in approximately 1.3 million screened newborns.


Racial and Ethnic Variability. Ireland, Australia, and Great Britain, 1 in 82,000. The lowest incidence is in Japan.

Molecular Pathology. At least nine specific genetic disorders have been recognized that affect one of the transsulfuration pathways that convert the sulfur atom of methionine into the sulfur atom of cysteine. This pathway is the chief route of disposal of methionine. The most common defect, cystathionine β-synthase deficiency, results in high levels of serum methionine that can be detected by newborn screening. One deletion mutation and two point mutations have been described.

Potential for Symptomatic Diagnosis. The potential for early clinical diagnosis is limited. Ocular abnormalities, because of their distinctive lens displacement, may lead to the diagnosis. The diagnosis should be considered in any child or young adult with thromboembolism affecting both the large and small arteries as well as the veins, particularly in association with developmental disabilities, mental retardation, or skeletal findings. Most patients, however, have nonspecific features so that definitive testing involving the measurement of serum or urine
Amino acids is not accomplished before the expression of more severe clinical symptoms.

**Genotype Phenotype Correlation.** Affected patients vary widely in the extent to which they manifest clinical abnormalities suggesting considerable genetic heterogeneity. Absent to relatively low residual activity (up to 10%) of cystathionine β-synthase has been noted among different families. The presence of some activity of the enzyme seems necessary for a clinical response to pyridoxine (vitamin B₆) administration. Individuals clinically responsive to pyridoxine generally have milder or more slowly progressive disease.

**Genetic Counseling.** The specific enzymatic defect must be ascertained. Obligate heterozygote carriers have 22% to 47% cystathionine β-synthase activity in cultured fibroblasts or long-term cultured lymphocytes. Prenatal diagnosis is available for cystathionine β-synthase deficiency using cultured chorionic villus cells or amniotic fluid cells to measure the activity of this enzyme.

**Severity and Variability Without Screening**

**Mortality.** Death has been reported within the first year of life. Approximately 50% of untreated individuals die by 25 years of age; death is frequently due to thromboembolic events.

**Developmental Disabilities.** Developmental delay is reported in 65% to 80% of untreated individuals.

**Physical Findings.** Marfanoid habitus, ectopia lentis, glaucoma, cataracts, osteoporosis with bone deformities, high palatal arch, and muscle weakness with a shuffling gait. Arterial or venous thromboses may involve the cerebral, pulmonary, renal, and myocardial circulation.

**Clinical Outcome With Screening and Treatment**

**Mortality.** Treatment seems to reduce the risk of thromboembolic episodes.

**Clinical Disability.** The incidence of mental retardation may be prevented or reduced. Ectopia lentis seems to be delayed, and the incidence of seizures is reduced.

**Variability.** Clinical variability remains despite therapy. However, the relationship between this variability and the underlying metabolic processes or compliance has not been ascertained. Not all affected individuals have elevated methionine levels. Other metabolic variants of homocystinuria include vitamin B₁₂, not cyanocobalamin) may be beneficial. Aspirin and dipyridamole have also been used to prevent thromboembolic phenomena.

**Screening Test Characteristics and Confirmation**

**Type of Test.** BIA to determine elevated levels of blood methionine. Newer methods include direct methionine assay by tandem mass spectrometry. Normal values are less than 2 mg/dL.

**Timing.** Elevation in levels of methionine may be minimal during the first 3 days of life until there is adequate protein intake (milk feedings), especially in patients responsive to vitamin B₁₂, who usually have some residual enzyme activity. This probably accounts for the difference in screening frequencies between the United States and United Kingdom, where screening specimens are obtained at 5 to 7 days. It may be preferable to screen for this disorder at 2 to 4 weeks of age. Early discharge at 24 or even 48 hours results in many missed cases and makes screening ineffective at this age.

**Stability of Specimen.** Unknown.

**Confirmation.** Quantitative serum or plasma amino acid determination. Plasma amino acids show increased levels of methionine and homocystine concentrations with reduced levels of cystine and absent levels of cystathionine. A urine organic acid profile with gas chromatography and mass spectrometry may be used to determine the presence or absence of methylmalonic acid.

**Accuracy of Screening Test**

False-Negative Rate. Only limited information is available. The false-negative rate seems to correlate with the time that the specimen was obtained and the level of residual synthase activity present (ie, the B₁₂-responsive form). The false-negative rate is increasing with earlier newborn discharges.

False-Positive Rate. About 1 in 5000 infants is found to have elevated blood methionine levels greater than 2 mg/dL (Mountain States Screening Program). In most instances, this is a benign temporary abnormality resulting from immaturity of the liver with transiently reduced enzyme levels or a high protein intake. Methionine levels may also be elevated in newborns with liver disease and in premature infants. The true-positive–false-positive ratio is approximately 1:20.

**Ongoing Studies.** Programs continue to evaluate the efficacy of screening and early treatment. Improvement in screening to decrease the numbers of missed cases is important. Ethnic variability, understanding different genetic types, and optimal treatment strategies need to be defined.

**Special Concerns and Issues**

Specialized care is required that includes the ability to monitor amino acids and provide nutritional assessment and planning. Doses of pyridoxine greater than 900 mg have been associated with neuropathy; however, these higher doses are usually not required for adequate treatment. Thromboembolic phenomena are more prone to occur during anesthe-
Phenylketonuria

State Newborn Screening Availability

Currently performed in all states, the District of Columbia, Puerto Rico, and the US Virgin Islands.

Brief Clinical Description

An autosomal recessive disorder of phenylalanine hydroxylation leading to accumulation of this amino acid. Patients with undiagnosed PKU have progressive developmental delay in the first year of life, severe mental retardation, seizures, autistic-like behavior, and a peculiar odor.

Genetics

**Chromosomal Map Location.** t-Phenylalanine hydroxylase (PAH), long arm of chromosome 12: 12q22–q24.

**Incidence.** One in 10,000 to 1 in 25,000 (United States); 1992 CORN data, 1 in 20,000 for classic PKU and 1 in 16,000 for classic and clinically significant hyperphenylalaninemia.

**Inheritance.** Autosomal recessive. Sex ratio: male = female.

**Racial and Ethnic Variability.** Considerable. Whites: 1 in 6000 in Ireland and Scotland; 1 in 8000 to 1 in 10,000 in former West Germany; 1 in 16,000 Italy; 1 in 6000 among Yemenite Jews; and 1 in 60,000 among Ashkenazi Jews. Less common among African-American and Asian families: China and Japan, 1 in 60,000. Non-PKU hyperphenylalaninemia was previously known as benign hyperphenylalaninemia: panethnic, 1 in 65,000 (average).

**Molecular Pathology.** Hyperphenylalaninemia is a generic phenotype distinguished by a persistently elevated phenylalanine concentration above the normal distribution that impairs the development of the central nervous system. Hyperphenylalaninemia can be caused by mutations at the locus encoding the enzyme PAH, at the loci for at least two enzymes in the pathway for the synthesis of tetrahydrobiopterin (BH2), the cofactor for the hydroxylation reaction, and at the locus for dihydropteridine reductase, the enzyme that generates BH2 from the oxidized product of the hydroxylation reaction. Mutations involving the PAH gene have been described, including missense mutations, deletions, and splice site mutations.

**Potential for Symptomatic Diagnosis.** The disease is rarely diagnosed before 6 months of age and usually only after mental retardation is obvious. Because of universal newborn screening, PKU may not be considered in the differential diagnosis in an infant with progressive developmental delay. Some cases are not diagnosed until the disease is discovered in a subsequent sibling by newborn screening.

**Genotype-Phenotype Correlation.** Both PKU and non-PKU hyperphenylalaninemia represent genetic defects at the PAH locus; the severity of the disease is generally related to the level of phenylalanine. Because there are numerous mutations, most patients (with the exception of inbred populations) are doubly heterozygous (ie, so-called compound heterozygotes) for different mutations at the PAH locus. There are other mutant alleles at the PAH locus that cause a lesser degree of hyperphenylalaninemia (ie, non-PKU hyperphenylalaninemia) with a lower risk of mental retardation.

**Genetic Counseling.** Prenatal diagnosis and carrier testing are available by DNA analysis using direct mutation analysis when identified in the proband or by linkage analysis. Infants of untreated affected mothers (maternal PKU) may have microcephaly, retardation, and congenital heart disease even when they are not affected by PKU. The efficacy of treatment to prevent fetal effects is under study, preliminary data show that treatment beginning before conception and continuing throughout pregnancy could be beneficial.

**Severity and Variability Without Screening**

**Mortality.** Classic PKU is not lethal, but data concerning institutionalized patients showed that their
life spans are reduced. Cofactor variants may lead to
death in childhood.

**Developmental Disabilities.** In 95%, IQ less than 50.
Some milder forms of hyperphenylalaninemia do not reduce intelligence.

**Physical Findings.** Convulsions, hyperactivity, and eczema are common.

**Clinical Outcome With Screening and Treatment**

**Mortality.** Not expected.

**Clinical Disability.** Normal early growth and development and normal range of intelligence with optimal dietary control, which needs to be maintained throughout life. Emerging data have indicated that some patients on less restrictive diets or taken off diet control have manifested late neuropsychiatric disturbances, agoraphobia, and memory deficits, and magnetic resonance imaging scans have showed white matter changes and deficits in the frontal cortex.

**Variability.** Cofactor-deficient variants may cause progressive neurologic deficits despite dietary restriction, and patients with these variants have a poorer prognosis. Patients with such variants require additional therapy. Hyperphenylalaninemia may not require treatment if the serum phenylalanine concentration remains less than 6 mg/dL.

**Possible Interventions.** Dietary restriction of phenylalanine with regular monitoring of serum phenylalanine levels is highly effective when begun before the infant is 4 weeks old (optimally as soon as possible) and should be continued indefinitely. Treatment of adults is strongly recommended and is required for women of childbearing age. Treatment after central nervous system damage has been sustained will not reverse retardation but may lead to some improvement in behavior control. Treatment may be costly and requires a special formula and a diet of low-protein foods. A nutritionist and a specially trained physician are necessary to coordinate therapy. Compliance is a problem for many adolescents. Cofactor variants need to be identified early and require combined therapy for dietary restriction and restoration of neurotransmitter homeostasis (e.g., bioperin, L-dopa, 5-hydroxytryptophan, and folinic acid).

**Screening Test Characteristics and Confirmation**

**Type of Test.** Measurement of the blood phenylalanine level by BIA using a dried blood spot (the original Guthrie test). Measurement by automated fluorometric assay is performed as the initial screen. Quantitative serum phenylalanine and tyrosine and biopterin, L-dopa, 5-hydroxytryptophan, and folinic acid measurement by automated fluorometric assay is performed as the initial screening test in 10 state screening laboratories. Screening cutoff level is greater than 4 mg/dL. Some states and jurisdictions, 3.0 mg/dL in 6 states, and greater than 2 mg/dL in the remaining 7 states (1992 CORN data).

**Timing.** Screening should occur in newborns older than 24 hours and younger than 7 days. Infants screened before 24 hours of life should be re-screened by 2 weeks of age to detect possible missed cases. This situation may be avoided by reducing the screening cutoff level to 2 mg/dL when specimens are taken before 24 hours of age, but this practice results in a marked increase in the false-positive rate and is not currently used in most state newborn screening programs. All infants should be screened at the time of nursery discharge or transfer regardless of age. Antibiotic treatment can affect the results by inhibiting bacterial growth in the Guthrie assay. Sick infants and premature infants should be screened by 7 days of age, regardless of feeding history or antibiotic treatment.

**Stability of Specimen.** Short-term stability and when frozen at -70°C is excellent. Stability under ambient conditions for several years has remained reliable.

**Confirmation.** Quantitative measurement of serum phenylalanine, tyrosine, urinary pteridines, and blood dihydropteridine reductase (to exclude cofactor variants that require additional specialized therapy). Quantitative phenylalanine and tyrosine are available in many laboratories; pterin measurements are available in a few centralized laboratories. Quantitative serum phenylalanine of more than 10 mg/dL (0.60 mmol/L) is most likely to be the classic variant; lower levels are more likely to reflect milder variants. All infants with levels above 6 mg/dL should be considered for dietary restriction of phenylalanine.

**Accuracy of Screening Test**

**False-Negative Rate.** Depends on the infant's age at testing and the cutoff used. With a cutoff of 4 mg/dL, approximately one third with PKU would be missed by a sample taken in the first 12 hours of life; 10% would be theoretically missed at 24 hours, 2.4% at 24 to 48 hours, and 0.15% after 48 hours. With a cutoff of 2 mg/dL, 2.6% would be missed when tested before 12 hours of age, but less than 1% would be missed at 24 hours.

**False-Positive Rate.** The false-positive rate using a 4-mg/dL cutoff is approximately 1 in 3300 samples. Lowering the cutoff rate to 2 mg/dL would more than triple the false-positive rate to 1 in 1000 samples for a true-positive-false-positive ratio of approximately 1:13.

**Ongoing Studies.** Current studies include assessments of long-term neuropsychiatric complications, the optimal maintenance level of phenylalanine, alternative dietary products, treatment of cofactor variants, and the effect of maternal preconceptional and postconceptional dietary management in the prevention of the maternal PKU syndrome. DNA analysis for detection of carriers and possible use of DNA technology on dried blood spots for newborn screening are being studied. A number of commercial companies are currently undergoing Food and Drug Administration studies of colorimetric screening kits for use with filter paper specimens.

**Special Concerns and Issues**

Reduction of phenylalanine levels requires protein restriction, costly specialized formulas and foods, and avoidance of aspartame (in diet drinks and non-glucose sweeteners). Follow-up requires specialized clinics (state or regional) and monitoring of serum levels of phenylalanine. There may be a lack of ade-
quorate public and third-party support for costs of treatment. Registries of affected girls and women are being developed to track those at risk for maternal PKU. Missed patients may include those screened before 24 hours of age, those not born in hospitals, those born in countries other than the United States, and those born before routine screening.

**Professional and Public Education**

Commonly provided by state programs, regulations, and/or law.

**GENERAL REFERENCES**


**SICKLE CELL DISEASES: SS, SC, AND S S–THALASSEMIA**

*State Newborn Screening Availability*

Currently performed in 42 states, the District of Columbia, Puerto Rico, and the US Virgin Islands.

**Brief Clinical Description**

A group of genetic disorders characterized by the production of abnormal hemoglobin β chains (eg, sickle cell disease HbSS). Affected individuals have lifelong hemolytic anemia with acute and chronic tissue damage secondary to the blockage of blood flow produced by the abnormally shaped red cells. Additional clinical manifestations include episodic vaso-occlusive crises, functional asplenia, sepsis, infections, splenic sequestration, and bone marrow aplasia. Other hemoglobinopathies can also be detected by current newborn hemoglobinopathy-screening methods.

**Genetics**

**Chromosomal Map Location.** β-Globin gene family, short arm of chromosome 11: 11p14.

**Incidence.** United States African-American live births: HbSS, 1 in 375; HbSC, 1 in 835; and HbS β-thalassemia 1 in 1667; 1992 CORN data, 1 in 40 000 to 1 in 60 000 HbSS in non-African-American newborns in California, New York, and Texas.

**Inheritance.** Autosomal recessive. Sex ratio: male = female.

**Racial and Ethnic Variability.** Most commonly found in persons of African ancestry, but it also affects persons of Mediterranean, Caribbean, South and Central American, Arabian, and East Indian ancestry. Prevalence of sickle cell disease (SS, SC, S β-thalassemia) in US populations: whites, 1 in 58 000; Hispanics from eastern states, 1 in 1100; Hispanics from western states, 1 in 32 000; Asians, 1 in 11 500; and Native Americans, 1 in 2700.

**Molecular Pathology.** The inherited disorders of hemoglobin fall into three overlapping groups: (1) structural variants, such as HbS and HbC, related to single-amino acid substitutions (ie, missense mutations); (2) thalassemias, all characterized by a reduced rate of synthesis of one or more of the globin chains of hemoglobin related to a variety of different mutational events; and (3) conditions in which fetal hemoglobin synthesis persists beyond the neonatal period, known collectively as hereditary persistence of fetal hemoglobin. The substitution of the amino acid valine for glutamic acid in HbS results in reduced deformability of the red cell (enhanced by acidosis and conditions of low oxygen tension) and, thus, its defective passage through the microcirculation, which is the basis for the vaso-occlusive manifestations of sickle cell disease. These structural changes of the red cell lead to shortened survival and chronic hemolytic anemia.

**Potential for Symptomatic Diagnosis.** Hemoglobin electrophoresis study of at-risk individuals is easily accessible. The clinical diagnosis is rarely made before 1 year of age, when symptoms will prompt
in investigation. Dactylitis (hand-foot syndrome) is an early manifestation. Overwhelming sepsis with untoward outcome may occur before any other symptoms, particularly within the first 2 years of life.

Genotype-Phenotype Correlation. Most individuals of western African ancestry show variable but significant clinical manifestations. A mild form of sickle cell disease (HbSS) exists in Saudi Arabia and India and is associated with unusually high fetal hemoglobin levels of 15% to 25%, which seem protective. The presence of the homozygous deletion form of α-thalassemia in association with HbSS (which occurs in 2% of African-American and Jamaican patients) also produces a milder clinical course. Other compound sickle diseases with severe features similar to those found in homozygous HbSS include HbSΔ Los Angeles and HbSO Arab. HbS/β-thalassemia is similar to HbSS; the β⁺ thalassemia compounds and HbSC cause milder symptoms.

Genetic Counseling. All are autosomal recessive disorders. Carrier testing is readily available by hemoglobin electrophoresis and other techniques. Solubility tests should not be used for screening or carrier testing. Prenatal and confirmational newborn screening diagnoses also are available by DNA analysis.

Severity and Variability Without Screening

Morbidity. Can be lethal especially in early infancy or childhood (10% mortality) because of overwhelming sepsis or splenic sequestration. Previous indications of reduced life span in adults are being reevaluated as a result of more aggressive and careful management; current predictions indicate an 85% chance that infants with HbSS will survive to 20 years of age.

Developmental Disabilities. Usually none. Cerebrovascular accidents or sequelae of meningitis may lead to neurologic deficits.

Physical Findings. Aseptic necrosis of bones, leg ulcers, neoproliferative retinopathy, serious infections, cerebral thromboses, renal concentrating defects, and delayed growth and sexual maturation.

Clinical Outcome With Screening and Treatment

Morbidity. With screening, penicillin prophylaxis, and heightened vigilance, early death and morbidity from overwhelming sepsis are significantly decreased. Death from acute splenic sequestration and aplastic crisis may be prevented or reduced.

Clinical Disability. Risks are lowered by aggressive treatment of infection, dehydration, and cerebral thromboses. Long-term clinical outcomes of patients identified by newborn screening programs are unclear because treatment remains prophylactic and symptomatic.

Variability. Marked clinical variability ranging from a few symptoms to more severe symptoms to death in early life. In part, clinical severity is also influenced by the presence of other mutations, i.e., combinations of other β chain mutations or thalassemic mutations.

Possible Interventions. Infants with HbSS or Sβthalassemia should begin penicillin prophylaxis at the time of diagnosis and by no older than 2 months. Immunization against pneumococcal, Hemophilus influenzae, and meningococcal infection should be given. Parent and patient education with rapid access to appropriate medical care for aggressive pain management, prompt recognition and early treatment of infections, management of dehydration and acidosis, blood transfusion therapy for selected patients (with severe anemia and cerebrovascular events), and judicious use of oxygen seem to reduce morbidity and mortality.

Screening Test Characteristics and Confirmation

Type of Test. Isoelectric focusing, hemoglobin electrophoresis on cellulose acetate followed by citrate agar or high-performance liquid chromatography (HPLC) on cord blood or a dried heel stick blood spot.

Timing. Timing is unimportant. Cord blood or heel stick blood can be obtained any time following birth.

Stability of Specimen. Filter paper specimens and cord blood are stable for several weeks frozen. Stability problems are more prevalent with cellulose acetate electrophoresis.

Confirmation. Hemoglobin electrophoresis using citrate agar at acid pH and isoelectric focusing or HPLC. The use of cellulose acetate alone is insufficient for differentiating HbS from hemoglobins D or G. Family studies and/or DNA analysis may be necessary to distinguish sickle cell trait from SB⁺ thalassemia, which depends on estimating the relative proportions of hemoglobins A and S and may be difficult to assess by electrophoretic methods; HPLC is also helpful.

Accuracy of Screening Test

False-Negative Rate. Unknown, because negative tests are usually not repeated unless the states have routine or discretionary second tests. Presumably, false-negative test results are quite low, with sensitivities of 93.2% on citrate agar gel electrophoresis and approximately 100% on isoelectric focusing.

False-Positive Rate. One in 3000; 97.9% of positive results were confirmed. One hundred percent specificity was noted in Massachusetts and Georgia newborn screening laboratories using isoelectric focusing on cord blood and additional filter paper specimen confirmations.

Ongoing Studies. Prospective studies regarding the impact of early diagnosis and vigorous treatment on prognosis; methods of treatment to prevent sickle crises: optimal use of blood products, oxygen, and vaccines; potential for gene therapy. Additional methods for improved screening include efficacy of HIPLC, immunologic approaches, and DNA analysis.

Special Concerns and Issues

Locating all infants with positive test results has been a problem in some areas. Coordinated care by specialized clinics (state or regional) or private primary care practitioners is needed, especially for adolescents and adults. Other concerns have included
stigmatization, confusion about the meaning of being a carrier, confidentiality, potential identification of nonpaternity, discrimination in the work place, and insurability. No uniformity exists in dealing with the high number of carrier infants detected by newborn screening programs. Thalassemia testing in Asian-Americans is also a problem. Screening programs identify and report all abnormal hemoglobin variants. Reports listing AF indicate there is more hemoglobin A than F, which may occur from a transfusion in a homozygous SS patient, and an absence of hemoglobin A may reflect homozygous β-thalassemia or a normal biological variation.

**Professional and Public Education**

Awareness is generally high, although many popular misconceptions exist. Excellent educational materials are provided by the US Department of Health and Human Services, state programs, comprehensive sickle cell centers, and local sickle cell organizations. Sickle cell support groups are available in most areas and serve as a resource for families.

**GENERAL REFERENCES**


**TOXOPLASMOSIS**

**State Newborn Screening Availability**

Currently performed as a part of the routine newborn screening profile in Massachusetts and New Hampshire by the New England Regional Newborn Screening Program.

**Brief Clinical Description**

Congenital toxoplasmosis is a protozoan infection that can result in blindness and mental retardation. Most infected newborn infants have no symptoms at birth, but by 20 years of age, as many as 85% of affected individuals have chorioretinitis, including many who were free of symptoms at birth.

**Incidence.** Estimated to range from 1 in 1000 to 1 in 8000 births in the United States; 1992 CORN and New England Regional Toxoplasma Working Group data, 1 in 8650 and 1 in 12,000 respectively.

**Epidemiology.** Toxoplasmosis gondii is ubiquitous in warm-blooded animals. Members of the cat family are definitive hosts. It remains one of the most common latent infections of humans throughout the world. Humans become infected either by consumption of poorly cooked meat (cysts are destroyed by boiling), or by accidental ingestion of sporulated oocysts from cat feces, soil, or contaminated food. Transmission by blood product contamination and from infected organ donors (heart and bone marrow) has been documented. Aside from placental infection from mother to fetus, toxoplasmosis is not communicable from person to person. Significant antibody titers have been detected in approximately 50% (United States) to 80% (France) of adults but varies considerably among people and animals in different geographic areas.

**Pathogenesis.** With the development of a normal immune response (humoral and cell mediated), infectious tachyzoites disappear from tissue. When a pregnant woman acquires the infection during gestation, the organism may be disseminated hematogenously to the placenta. When this occurs, infection may be transmitted to the fetus transplacentally or during vaginal delivery. Approximately 50% of untreated women who acquire the infection during gestation transmit the parasite to their fetuses. The incidence of transmission is least in early gestation and greatest in late gestation. The transmission rate is approximately 17% during the first trimester, and disease in the infant is usually severe. If the infection is acquired by the mother in the third trimester and is not treated, approximately 65% of fetuses are infected, and involvement may be mild or inapparent at birth. Congenital infection also may be transmitted by an asymptomatic immunosuppressed woman (eg, those treated with steroids and those with human immunodeficiency virus) to the fetus.
immunodeficiency virus infection). These different rates of transmission are most likely related to placent al blood flow, the virulence and amount of T gondii acquired, and the immunologic ability of the mother to restrict parasitemia.

Potential for Symptomatic Diagnosis. Extremely variable. Data in the literature indicate that more than half of congenitally infected infants are considered healthy in the perinatal period, but almost all have ocular involvement later in life. The New England Regional Toxoplasmosis Working Group reported that only 2 (4%) of 52 confirmed congenital cases detected by newborn screening were identified by initial clinical examination in the newborn period. Symptoms in the newborn period range from relatively mild signs, such as prematurity, small size for gestational age, peripheral retinal scars, persistent jaundice, mild thrombocytopenia, and cerebrospinal fluid pleocytosis, to the classic triad of chorioretinitis, hydrocephalus, and cerebral calcifications. Neonatal neurologic findings such as convulsions and hydrocephalus may be associated with substantial cerebral damage.

Prenatal Testing and Counseling. In women with normal immune systems, congenital toxoplasmosis generally does not recur. Fetal transmission essentially only occurs with an acute infection in the pregnant woman. The Sabin-Feldman dye test and the immunoglobulin G (IgG) immunofluorescent antibody (IFA) measure the same, primarily IgG, antibodies, and the titers tend to be parallel. Such antibodies appear 1 to 2 weeks after infection, reach high levels, generally more than 1:1000 IU after 6 to 8 weeks, and then decline over months to years. Low titers (1:4 to 1:64) usually persist for life. Approximately half of the commercially available IFA kits tested have been found to be improperly standardized and may yield significant numbers of false-positive and false-negative results. The IgM IFA is useful for the diagnosis of acute infection, because IgM antibodies appear earlier (often by 5 days after infection) and disappear sooner than IgG antibodies. More sensitive tests for the determination of a recent infection in pregnant women include the double-sandwich IgM enzyme-linked immunosorbent assay (ELISA). For newborns, the IgM-specific ELISA on filter paper cards is the test used and detects approximately 75% of infants with congenital infection. These tests are best performed in reference laboratories.

Pregnant women, particularly those who do not have specific antibodies to T gondii before pregnancy, should be counseled to avoid eating meat that is not cooked and contact with oocysts found in cat feces, kitty litter, and soil. Cats that are kept indoors and fed prepared diets rather than fresh uncooked meat should not contract encysted T gondii and shed oocysts. Serologic screening and treatment of newly infected pregnant women during gestation can also reduce the incidence and perhaps the manifestations of congenital toxoplasmosis.

Severity and Variability Without Screening

Mortality. Premature births, stillbirths, and neonatal mortality have been observed; the incidence is ill defined.

Developmental Disabilities. On the basis of 152 patients with clinically apparent disease in the first year of life, the following data were found: 94% chorioretinitis, 50% convulsions, 50% intracranial calcifications, and 28% hydrocephalus. At 4 years of age, for 101 of these same patients: 85% mental retardation, 80% convulsions, 60% neurologic impairment (spasticity and palsies), 50% impaired vision, 40% hydrocephalus or microcephalus, and 15% deafness. By age 20 years, 85% of patients had chorioretinitis, with severe visual impairment in about 50%.

Physical Findings. Additional physical findings include hepatosplenomegaly, lymphadenopathy, jaundice, and thrombocytopenia.

Clinical Outcome With Screening and Treatment

Mortality. All deaths are not prevented. Prematurity and stillbirths will not be prevented unless disease is detected prenatally and maternal treatment is initiated.

Clinical Disability. Severe intrauterine disease occurs in some infants, particularly those infected in the first trimester. However, 50 of 52 infants (New England Regional Toxoplasma Working Group) were asymptomatic at birth by clinical examination, although 19 (40%) of 48 infants had abnormalities of the central nervous system or the retina, which were found on more detailed initial examinations as the result of positive newborn screening results. After treatment, only 1 of 46 children had a neurologic deficit. Thirty-nine children had follow-up ophthalmologic examinations from 1 to 6 years of age; 10% had eye lesions that may have developed postnatally despite treatment.

Variability. The outcome of neurologic and ophthalmologic sequelae following neonatal treatment requires further evaluation.

Possible Interventions. Treatment regimens include combinations of pyrimethamine, sulfadiazine or triple sulfonamides, and spiramycin, with leucovorin prophylaxis for potential pyrimethamine toxicity. Treatment may be effective in interrupting acute disease that progresses to damage vital organs. The length of therapy and optimal therapy are under investigation using several combination regimens.

Screening Test Characteristics and Confirmation

Type of Test. IgM-specific ELISA using filter paper cards.

Timing. Timing is unimportant.

Stability of Specimen. Not determined.

Confirmation. Screening test results are confirmed by serologic testing of the mother and infant. Inconclusive results may require tissue culture and peritoneal inoculation of mice with blood and/or spinal fluid.

Accuracy of Screening Test

False-Negative Rate. Reported sensitivity is 75%.
False-Positive Rate. New England Regional Newborn Screening Program confirmed 52 of 100 cases that were positive on initial screening. The true-positive–false-positive ratio was 1:2.


Special Issues and Concerns

About 45% to 50% of infants have central nervous system and ophthalmologic findings at birth by detailed study, although only a small percentage (4% in the New England Study) had obvious clinical manifestations that would have led to more in-depth examinations. Improvement of the reported low sensitivity rate and long-term outcomes with neonatal treatment is in progress. Early studies suggest a significant reduction in neurologic and ophthalmologic deficits; data are needed concerning cognitive development. Serologic testing is not uniform in many commercial laboratories.

Professional and Public Education

Awareness is generally limited. Screening of pregnant women is controversial and not routinely performed.

GENERAL REFERENCES


TYROSINEMIA

State Newborn Screening Availability

Currently part of the routine newborn screening program in two states; five other states with programs reported in the 1992 CORN data report are considering discontinuing (or have discontinued) the program.

Brief Clinical Description

Neonatal tyrosinemia, type I tyrosinemia (tyrosinosis), and type II tyrosinemia (Richner-Hanhart syndrome) all show elevated levels of tyrosine and can be detected by newborn screening. Clinical features range from mild retardation and linguistic delays (neonatal form) to acute failure to thrive, vomiting, diarrhea, hepatomegaly, and ensuing liver disease with death from liver failure in acute tyrosinosis; chronic liver disease, renal tubular dysfunction (Fanconi syndrome), and hypophosphatemic rickets in chronic tyrosinosis; and characteristic corneal lesions and hyperkeratosis in Richner-Hanhart syndrome.

Genetics

Chromosomal Map Location. Fumarylacetoacetase hydroxylase (FAH): 15q23–q25 (type I tyrosinemia); and tyrosine aminotransferase (TAT): 16q22–q24 (type II tyrosinemia).

Incidence. CORN data from 1991 indicate 2 confirmed diagnoses in 94,000 screened newborns; no confirmed cases were identified in 232,000 screened cases in the 1992 CORN report. Neonatal tyrosinemia has the highest prevalence in premature infants: 1 in 250 infants weighing less than 2500 g and 1 in 500 infants weighing more than 2500 g. (Belgian newborn screening program). The highest incidence is in Canadian Inuits who do not breastfeed their infants (1 in 16). Tyrosinosis (type I tyrosinemia) has an incidence of 1 in 120,000 in Sweden and 1 in 100,000 in Norway. The highest prevalence is in the French-Canadian population of Quebec, with an overall incidence of 1 in 12,500, 1 in 685 in the Lac-St Jean region of Quebec. The incidence for Richner-Hanhart syndrome (type II tyrosinemia) has not been established.


Racial and Ethnic Variability. Mostly white. The neonatal form is most prevalent in Canadian Inuits. Tyrosinosis is most prevalent in the French-Canadian population in Canada and Northern Europe (Scandinavia). Cases of Richner-Hanhart syndrome have been described in several countries including the United States, Canada, Italy, countries of northern Europe, Turkey, United Arab Emirates, and Japan.

Molecular Pathology. Neonatal tyrosinemia and increased excretion of tyrosine and its metabolites are not uncommon, particularly in preterm infants. Decreases in incidence have been noted with a diet of human and low-protein milk ("humanized" cow milk). It is generally assumed that this disorder is caused by a relative deficiency of p-hydroxyphenylpyruvate, stressed by high-protein diets with resulting high tyrosine and phenylalanine levels. Others have suggested a mild defect in TAT activity.

Most cases of type I tyrosinemia (tyrosinosis) are caused by a deficiency of FAH. This disorder, although not a primary disorder of tyrosine metabolism, is accompanied by elevated levels of tyrosine and its metabolites, which inhibit many transport functions and enzymatic activities. It has been proposed that the degree of residual FAH activity determines whether the disease will be acute or chronic in the affected patient; patients with the acute form show no immunologically cross-reactive protein in

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the liver, whereas those with the chronic form have variable amounts of enzyme activity. Highest levels of FAH are found in liver cells but are also present in chorionic villi, amniocytes, fibroblasts, lymphocytes, and erythrocytes.

Type II tyrosinemia (Richner-Hanhart syndrome) is associated with a deficiency of hepatic TAT, the rate-limiting enzyme of tyrosine catabolism. Tyrosinemia, tyrosinuria, and increases in urinary phenolic acids, N-acetyltirosine, and tyramine persist for life. The metabolism of other amino acids and renal and hepatic function are otherwise normal.

Potential for Symptomatic Diagnosis. Extremely difficult unless there is a high index of suspicion resulting in the detection of increased levels of tyrosine in plasma or urine by quantitative amino acid analysis. Clinical findings in neonatal tyrosinemia are nonspecific. Infants with persistent neonatal tyrosinemia may be somewhat lethargic and have difficulty swallowing, impaired motor activity, prolonged jaundice, and increased levels of galactose, phenylalanine, histidine, and cholesterol. Mild acidosis may be present in about half of the infants. Mild retardation and decreased psycholinguistic abilities have been noted in some studies.

Type I tyrosinemia in the acute form is characterized by failure to thrive, vomiting, diarrhea, a cabbage-like odor, hepatomegaly, fever, jaundice, edema, melena, and progressive liver disease. If untreated, death from liver failure may occur in the first year of life. The chronic form is similar but with milder features characterized by chronic liver disease and renal tubular dysfunction (Fanconi syndrome) with hypophosphatemic rickets. Other features have included hypertrophic obstructive cardiomyopathy, abdominal crises, polyneuropathy, hypertension, and hepatoma (a late complication in one third of patients). Death occurs during the first decade of life. Increased levels of tyrosine are present in blood and urine. Urinary tests for succinylacetone and tissue analysis for FAH establish the diagnosis.

Type II tyrosinemia is a distinctive oculocutaneous syndrome. Eye findings may be limited to lacrimation, photophobia, and redness. Signs may include mild corneal herpetiform erosions, dendritic ulcers, and, rarely, corneal and conjunctival plaques. Neovascularization may be prominent. Long-term effects include corneal scarring, nystagmus, and glaucoma. The skin lesions usually begin with or after the eye lesions. Skin findings may begin as painful, nonpruritic blisters or erosions that crust and become hyperkeratotic and are usually limited to the palms and soles, especially the tips of the digits, and to the thenar and hypothenar eminences. They may be linear or subungual. A skin biopsy is not diagnostic and may show nonspecific hyperkeratosis, acanthosis, and parakeratosis. The skin lesions may be difficult to distinguish from any of the more common forms of keratosis. Mental retardation is an inconstant feature; mild to moderate retardation, self-mutilating behavior, disturbances of fine-motor coordination, and language deficits have been reported. Tyrosinemia is the diagnostic feature of this disorder.

Severity and Variability Without Screening

Mortality. Death from complicating liver failure occurs in untreated patients during the first year of life in the acute form and during the first decade of life in the chronic form of type I tyrosinemia.

Developmental Disabilities. Mild developmental and language delays have been noted in all forms of tyrosinemia but are quite variable. Mental retardation is an inconstant feature.

Physical Findings. Hepatomegaly is an inconstant feature of neonatal tyrosinemia, present in type I disorders with associated jaundice and abnormal liver function and absent in type II disorders. Type II tyrosinemia has characteristic ocular and cutaneous findings that are not present in the neonatal period but generally become apparent in infancy or early childhood.

Clinical Outcome With Screening and Treatment

Mortality. Insufficient data are available to evaluate the effects of early treatment in patients detected by newborn screening. A decrease in early mortality from progressive liver failure has been noted in type I tyrosinemia with diets low in tyrosine, phenylalanine, and methionine. Long-term outcomes are less optimistic.

Clinical Disability. Most cases of neonatal tyrosinemia, especially those seen in small preterm infants, may be transient and controlled by reducing the protein intake to 2 to 3 g/kg per day or by breast-feeding. Occasional patients respond to ascorbic acid supplementation. Palliation in type I disease has relied on a diet low in tyrosine, phenylalanine, and...
methionine. Liver transplantation has been performed in an effort to prevent hepatoma but is not effective in treating all the metabolic abnormalities. Elevated levels of succinylacetone persist. Therapy with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,2-cyclohexanedione decreases succinylacetone production and has shown promise if started early in the course of the disease. Therapy with a diet low in tyrosine and phenylalanine is curative in type II tyrosinemia.

**Variability.** Early diagnosis should lead to the initiation of dietary restriction, but long-term outcome in type I remains uncertain. An elevated newborn screening test result for tyrosine requires confirmation and additional testing, because it may be caused by other metabolic disorders (eg, fructose and galactose enzyme deficiencies), giant cell hepatitis, neonatal hemochromatosis, and neonatal infections.

**Possible Interventions.** Dietary restriction has been the mainstay of therapy. Liver transplantation has been beneficial in type I disease. Other forms of therapy to reduce levels of succinylacetone are under investigation. Patient follow-up requires maintaining adequate protein to support growth and repeated measurements of blood tyrosine, methionine, α-feto-protein, and blood and urine succinylacetone.

**Screening Test Characteristics and Confirmation**

**Type of Test.** BIA of tyrosine on dried blood spots. Abnormal levels are reported as greater than 6 mg/dL; Georgia uses a level of greater than 12 mg/dL.

**Timing.** Neonatal period, but the optimal time for study is unclear. Presumably, it is best if measurements are obtained 48 to 72 hours after milk feeding.

**Stability of Specimen.** Has not been determined specifically for tyrosine but should be similar to that of phenylalanine.

**Confirmation.** The optimal approach is complex and requires amino acid quantitation of blood and urine for tyrosine as well as other amino acids and metabolites. Confirmation of neonatal tyrosinemia depends on the presence of elevated levels of tyrosine and phenylalanine; type I tyrosinemia has elevated levels of urine succinylacetone and nonspecific aminooxyacidaemia and requires tissue analysis (fibroblasts, erythrocytes, lymphocytes, or liver) for FAH activity; type II tyrosinemia shows elevation of tyrosine only in blood and urine.

**Accuracy of Screening Test**

False-Negative Rate. Undetermined.

False-Positive Rate. CORN data from 1991 showed an initial positive screening test in 288 of 94 000 newborns tested (1 in 330) with 2 positive confirmed cases. The true-positive to false-positive ratio is 1:144. Available data on second screens performed between 1 and 4 weeks of age showed 85 positive tests in 155 365 infants (1 in 1828); no cases of tyrosinemia were confirmed among this group.

**Ongoing Studies.** The incidence and pathogenetic mechanisms of specific disorders associated with elevated levels of tyrosine require clarification. The consequences of early diagnosis and treatment for type I tyrosinemia (the most formidable disorder in this group) should be of benefit. Other modes of therapy seem to be required to offset the other metabolic abnormalities seen in this disorder.

**Special Concerns and Issues**

The confirmation of the exact cause of elevated tyrosine levels requires referral and evaluation by an expert in the field. Outcome with treatment remains variable.

**Professional and Public Education**

Physician and public awareness of these relatively uncommon disorders, outside the French-Canadian experience, is minimal. Educational efforts are required.

**GENERAL REFERENCES**


**ADDITIONAL NEWBORN SCREENING INFORMATION**

The following disorders are not currently part of state newborn screening programs. Several commercial newborn screening programs test for a battery of other metabolic disorders using dried blood filter paper blots. Some university-based laboratories and commercial laboratories are able to test blood and urine specimens for specific metabolic disorders as well. Consideration for newborn screening for metabolic disorders may include a previously affected child, a positive family history, the history of a previous infant who died in early infancy with a suspected metabolic disorder, or parental consanguinity (ie, first-cousin marriages), particularly in at-risk ethnic populations.

Newborn screening for adenosine deaminase (ADA) deficiency, arginase deficiency (AD), urea cycle defects, Duchenne muscular dystrophy (DMD),
glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, pyroglutamic aciduria, medium-chain acyl-CoA dehydrogenase deficiency (MCAD), and other organic acidemias are available through a few commercial laboratories. Neuroblastoma has also been suggested as a target for universal screening on young infants 3 to 6 months of age.

ADA Deficiency; Autosomal Recessive Severe Combined Immunodeficiency Disease

Autosomal recessive deficiency of ADA causes abnormalities in purine nucleoside metabolism that are selectively toxic to lymphocytes. Most patients with ADA deficiency are severely lymphopenic and lack both cell-mediated (T-cell) and humoral (B-cell) immunity, resulting in severe combined immunodeficiency disease. Untreated children with ADA usually die before 2 years of age of overwhelming and opportunistic infections. Accumulation of toxic metabolites can disturb neurologic function. The actual prevalence of this condition has not been determined, but estimates of frequency are about 1 in 225 000. Enzymatic activity of ADA can be measured from dried blood filter paper blots. Bone marrow transplantation, erythrocyte replacement therapy, enzyme replacement with polyethylene glycol-ADA, and, more recently, recombinant gene transfer have been effective in improving immune function and correcting the biochemical abnormalities. This disorder also has been the first condition successfully treated with recombinant gene therapy. Incorporation of screening for this disorder in a pilot program may help provide data concerning prevalence and the cost-benefit ratio of screening for rare but potentially treatable disorders.

AD and Other Urea Cycle Defects

As a group, the disorders of the urea cycle are estimated to have an incidence of at least 1 in 60 000. Most affected patients with urea cycle disorders become severely ill with neonatal hyperammonemic coma, which usually occurs before the results of neonatal screening are available. However, milder forms of the disorders exist that have less severe and later onset of symptoms and may benefit from early detection and treatment through newborn screening. The Guthrie blood test using appropriate Bacillus subtilis auxotrophs has been proposed for neonatal screening for argininosuccinic acid synthetase deficiency (ASD), argininosuccinic acid lyase deficiency (ALD), and AD. These disorders are associated with marked accumulation of citrulline, argininosuccinic acid, and arginine, respectively. Moderate increases in citrulline levels are also noted in ALD and AD. Because many patients with ASD and ALD have severe forms of the disorder, and neonatal hyperammonemic coma will develop, screening may not be of benefit for therapeutic purposes in these cases. However, patients with milder and later-onset disease may benefit from early detection and treatment with restricted protein intake, supplemental arginine, and, in cases of ASD, drugs that use alternative means for excess nitrogen excretion. Previous urine screening programs in Massachusetts and Quebec found an incidence of ASD of 1 in 73 000; ALD, 1 in 250 000; and AD, 1 in 225 000. In contrast to ASD and ALD, AD is not usually associated with symptomatic neonatal hyperammonemia but results in progressive spastic tetraplegia (with the lower limbs more severely affected than the upper limbs), seizures, psychomotor retardation, hyperactivity, and growth failure. Patients with AD would more likely benefit from early detection and treatment with restriction of dietary protein intake; the true incidence of this rare disease is unknown. Two other disorders of the urea cycle, carbamylphosphate synthetase deficiency and ornithine transcarbamylase deficiency, result in massive neonatal hyperammonemia in most affected patients. Mild and later-onset forms of these disorders are also known. Patients with these deficiencies have reduced plasma levels of citrulline. A newborn filter paper spot test that measures arginase activity by a fluorescent assay and citrulline by tandem mass spectrometry is being piloted commercially. Confirmation is by quantitative measurement of arginase activity and plasma amino acid profiles. The usefulness of neonatal screening testing for these disorders seems promising for AD and the mild and later-onset forms of the other disorders, but detection of the severe forms remains difficult.

Duchenne Muscular Dystrophy

DMD is the most common childhood form of muscular dystrophy resulting in a progressive deterioration of muscles beginning in infancy and leading to death in the second or third decade of life. It is inherited as an X-linked trait, and with few exceptions only boys are affected. The Duchenne-Becker gene is now known to be one of the largest human genes characterized thus far and has been mapped to the short arm of the X chromosome (Xp21). This gene encodes a protein, dystrophin, the properties and distribution of which suggest a key role in maintaining the integrity of myofibrillar structure and function. A wide variety of mutational defects with partial or complete gene deletions has been noted in the majority of patients. Distribution is worldwide, with an incidence of 1 in 3000 to 1 in 5000 male live births for DMD and 1 in 18 500 male live births for Becker muscular dystrophy (BMD). There is no medical treatment for DMD, which has a progression rate that is variable, although early death in the second or third decade of life is the rule. An allelic form of BMD is a similar but more slowly progressive disorder with longer survival. Patients with DMD and BMD may be at risk for malignant hyperthermia.

Newborn screening using dried blood filter paper blots is available through a voluntary commercial laboratory (Supplemental Newborn Screening Program in Pennsylvania) that also includes a Muscular Dystrophy Association pilot screening program in Puerto Rico and hospitals in New York and Texas. The voluntary program in Germany tests infants between 4 weeks and 1 year of age. Pilot programs in France (Lyon), Belgium (Antwerp), Canada (Manitoba), and the United Kingdom (Wales) also test newborns. Testing involves the determination of creatine kinase (CK) by fluorescent spot assays. Normal
specimens exhibit no fluorescence, whereas specimens with CK levels greater than 500 U/L exhibit fluorescence. Confirmation requires CK activity in serum with an isoenzyme pattern. The dystrophin status of muscle biopsy specimens by immunoblot and immunofluorescent assays helps confirm disease in patients without identifiable DNA mutations and distinguishes the more severe DMD from the milder BMD when DNA mutation analysis is not informative. An initial CK elevation was noted in 3 of 1000 screened newborns, with 4.5% having a persistent elevation on another specimen with a CK-MM or CK-MB isoenzyme pattern giving a true-positive–false-positive ratio of 1:17. The worldwide experience with DMD and BMD based on 935 000 screened newborns, with 4.5% having a persistent elevation, was noted. An initial CK elevation was noted in 3 of 1000 screened male infants was summarized in the 1993 report of the European Neuromuscular Center Workshop. The recognizable benefit to patients, their families, and society in the absence of any currently available treatment remains a hotly debated and controversial matter. Concerns regarding psychologic and intrafamilial distress with presymptomatic diagnosis (some 40% of cases occur in families with no previously affected individuals) have been raised. Conversely, the availability of early diagnosis may enable families to make practical decisions about the life of a child with special needs and to avoid prolonged "diagnostic odysseys." Genetic counseling and testing of identified families and at-risk family members may be of benefit for some families.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

G6PD deficiency results in a defect in the pentose phosphate pathway that normally helps protect hemoglobin from oxidant hemolysis. The prevalence and gene frequency is 1 in 10 African-Americans, 1 in 10 Mediterranean families (Italian, Greek, and Middle Eastern), and 1 in 50 southeast Asians. Clinical disorders associated with the more severe Mediterranean and Asian forms of the deficiency include neonatal hyperbilirubinemia, chronic congenital nonspherocytic hemolytic anemia, and drug- or viral-induced hemolytic anemia. In the African-American form, acute hemolytic anemia may occur with infection and certain oxidant drugs; the clinical picture is less severe, because there is some activity of the G6PD enzyme. It is inherited as an X-linked recessive trait. Treatment requires avoidance of oxidant drugs such as antimalarials, sulfonamides, nitrofurans, and naphthalene. Fava beans provoke hemolysis in Mediterranean families. Patients should avoid the use of aspirin. The screening method is based on a fluorescent spot test that measures the activity of the G6PD enzyme. Extensive screening is being performed in Greece and southeast Asia. Confirmation requires quantitative measurement of serum G6PD activity and G6PD electrophoresis for specific isoenzyme typing.

Pyroglutamic Aciduria (Oxoprolinuria or Glutathione Synthetase Deficiency)

The reduced form of glutathione (GSH), an intermediary in the γ-glutamyl cycle, is normally found in erythrocytes in high concentrations. GSH plays an important role in erythrocyte metabolism and in the transport of amino acids across membranes. It also serves as a reductant of toxic peroxidases protecting hemoglobin and other protein sulfhydryl groups against the destructive effect of oxidation. Deficient levels of GSH have been reported in patients with pyroglutamic aciduria due to glutathione synthetase deficiency. Symptoms characteristic of these disorders include recurrent episodes of vomiting, diarrhea, and abdominal pain and, if untreated, may result in congenital nonspherocytic hemolytic anemia, metabolic acidosis, progressive decline in psychomotor skills with mild mental retardation, and pyroglutamic aciduria. Prevalence is estimated at 1 in 100,000. Inheritance is autosomal recessive. Screening is based on a colorimetric assay of a blood spot that measures the presence of GSH. Confirmation requires urine organic acid analysis by gas chromatography and mass spectrometry. Vitamin E therapy may be beneficial. The exact prevalence, therapeutic modalities, and long-term outcomes remain uncertain.

Medium-Chain Acyl-CoA Dehydrogenase Deficiency

MCAD is an autosomal recessive condition resulting in a defect of fatty acid β oxidation usually triggered by fasting or infection. The clinical presentation is subtle and variable and can present similarly to other defects of fatty acid oxidation with symptoms of acute encephalopathy and hepatomegaly that mimic Reye's syndrome. Episodes characterized by nonketotic hypoglycemia can be so rapid and fulminating that the infant seems to have an apparent life-threatening event or sudden infant death syndrome. Approximately 30% of patients with MCAD die during the first clinical episode; it has been reported to account for 2% to 3% of all deaths attributed to sudden infant death syndrome. Prevalence has been reported as between 1 in 10 000 and 1 in 25 000 in the United Kingdom. The common missense mutation A985G accounts for more than 85% of the mutations and can be detected in the newborn by DNA analysis on Guthrie cards. The overall homozygous prevalence of the common mutation was noted to be 1 in 6400 in white populations. Heterozygote frequencies were noted to be 1 in 40 in Birmingham, United Kingdom, 1 in 71 in Melbourne, Australia, and 1 in 107 in Houston, TX. MCAD has not been detected in Japanese families. The prevalence in more heterogeneous populations in the United States is not known, but in Pennsylvania the incidence from newborn screening was 1 in 6900. The cost and feasibility for the use of newborn blood spots for DNA analysis (for this and other genetic disorders) in a universal newborn screening program remain unclear. Tandem mass spectrometry to measure octanoylcarnitine on the filter paper blood spot (normally not present) is the initial screening modality, with a urine organic acid profile and DNA mutation analysis available for confirmation. Treatment includes avoidance of fasting, reduction of dietary fat, and carnitine supplementation. Because this disorder is relatively common and represents a potentially
recognizable cause for acute life-threatening events in infants, pilot programs will be helpful in providing important information about the natural history of this disorder and the feasibility of incorporation in a newborn screening program.

Organic Acidemias

Methylmalonic Acidemias. A group of defects associated with a primary enzyme deficiency in the breakdown of organic acids or a number of defects in vitamin B₁₂ transport or activation of organic acids. Neonatal presentation occurs with early onset disease of metabolic acidosis; milder forms with onset in infancy are associated with mild to severe acidosis, neurologic symptoms, and failure to thrive. Combined frequency: 1 in 50 000. Treatment involves dietary protein restriction, special dietary formulas, and/or hydroxocobalamin supplementation.

Propionic Acidemia. Deficiency of the enzyme propionyl-CoA carboxylase that leads to a defect in the breakdown of organic acids. Presentation occurs within the first days of life, with poor feeding, vomiting, seizures, metabolic acidosis, and coma. Occasionally, later onset occurs with ketoacidosis and developmental retardation. Autosomal recessive. Frequency: 1 in 50 000. Treatment involves dialysis, protein restriction, special dietary formulas, and carnitine and biotin supplementation.

Isovaleric Acidemia. Autosomal recessive defect in the breakdown of organic acids caused by a deficiency of isovaleryl-CoA dehydrogenase. This disorder may present in the newborn period as an acute episode of metabolic acidosis with vomiting and coma (characteristic urine odor of sweaty socks) or as a chronic intermittent form with recurrent episodes of acidosis. Infants who survive the acute newborn form later exhibit the chronic form. Frequency 1 in 50 000. Treatment with moderate protein restriction, special dietary formulas, and carnitine and/or glycine supplementation generally results in normal development.

Glutaric Acidemia Type I. Another autosomal recessive defect in the breakdown of organic acids presenting within the first years of life with impaired movement and muscle tone dystonia and macrocephaly. After the initial onset, the neurologic course is gradually progressive, with periodic episodes of acidosis, vomiting, seizures, and coma. The highest frequency is noted among the Amish population in Lancaster County, PA; the general frequency is estimated at 1 in 30 000. Protein restriction, special dietary formulas, and riboflavin and carnitine supplementation may be beneficial.

The above organic acidemias can be screened on filter paper blood spots for various carnitine esters (e.g., propionyl carnitine and isovaleryl carnitine) using tandem mass spectrometry. These compounds would normally not be present. Confirmation requires urine organic acid profiles and specific quantitative enzyme assays. The value of screening for rare metabolic disorders remains unclear, particularly when many forms of these disorders present clinically in the first few days of life.

Neuroblastoma. Pilot projects for screening for neuroblastoma are currently underway in Quebec, Japan (Sapporo, Kyoto, and currently as a nationwide program) and the northern region of England (Newcastle-on-Tyne, United Kingdom). Some sporadic screening programs are being carried out in the United States (Baltimore, MD, Houston, TX, and Minnesota). Screening has been performed using urine-saturated filter paper at 3 weeks and 6 months of age (Quebec) and 6 months of age (Japan and United Kingdom) for the quantitative analysis of the catecholamine metabolites vanillylmandelic acid and homovanillic acid using a urine organic acid profile or HPLC. The prevalence rates of neuroblastoma were approximately 1 in 15 700 (Quebec), 1 in 10 800 (Japan), and 1 in 10 400 (United Kingdom). The survival rate of the large Japanese cohort detected at 6 months of age was 97% (348 of 357 cases). Feasibility, cost effectiveness, technical problems in the laboratory screening procedure, natural biological properties of the tumor itself, and acceptability and outcome of screening programs remain to be resolved.

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Newborn Screening Fact Sheets

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