

National Coordinating Center for Genetics and Newborn Screening Regional Collaboratives

MCHB/HRSA Funded Cooperative Agreements

Michael S. Watson, PhD
February 13, 2006

National Coordinating Center: Genetics and NBS Regional Collaboratives

- Supports the seven Regional Collaborative efforts to identify issues specific to utilization of genetics and newborn screening services at all levels
- Seeks to minimize duplication of efforts
- Identifies “best practices” developed by regions
- Furthers information exchange and professional collaboration
- Facilitates focus on MCH and program goals
- Seeks to maximize interregional collaboration
 - Language and terminology compatibility
 - Involves genetics, public health, state, business, academia

Coordinating Center: Advisory Committee

- Jonathan Zonana, MD Chair
- Harvey Levy, MD
- Kenneth Pass, PhD
- Sharon Terry
- Brad Therrell, PhD
- Steven Downs, MD
- Tracy Trotter, MD
- Mendel Tuchman, MD, PhD (SIMD)
- April Studinsky, MS (NSGC)
- Norman Kahn, MD (AAFP)
- Alissa Johnson (NCSL)
- Fan Tait, MD (AAP)
- Nancy Green, MD (MOD)
- Christopher Kus, MD, MPH (AMCHP)
- Cheryl Aldrich, RN, CPNP (NAPNAP)
- Stephen Groft, DPharm (ORD)
- Aileen Kenneson, PhD (CDC)
- Lauren R. Ramos, MPH (ASTHO)
- Lisa Wise, MS (Genetic Alliance)
- James Hanson, MD (NICHD)
- Willarda Edwards, MD
- Michele Lloyd-Puryear, MD, PhD (MCHB/HRSA)
- Marie Mann, MD, MPH (MCHB/HRSA)
- Michael Watson, PhD (ACMG)
Project Director
- Judith Benkendorf, CGC
Project Manager (ACMG)

ACMG Plans for NCC

- Develop centers of genetics (COGs) and provider networks
- Facilitate data collection
 - NIH rare disease centers
 - CDC genomics centers
 - Advocate for national collaborative study group system for rare genetic disease
- Involve national programs to which ACMG, AAP, and AAFP link
 - CPT code development
 - JCAHO role in hospital activities related to NBS
- Information from projects with overlapping interests
- Facilitate collaboration and dissemination of best practices

NCC Projects ¹

- Building the Business Case
- Developing a Defined Network of Genetic Service Providers
- Management guidelines for primary care, specialty and genetics services providers
- Identifying NBS pilot studies
 - Facilitating links between researchers/providers and screening laboratories
- Improving screening laboratory performance
- Education (primary care → specialists)

Building the Business Case¹

- System problems
 - System problems amenable to repair
 - CPT
 - RUC
 - ICD
 - SnoMed
- New technology and knowledge problems
 - Outcome studies to support use
 - Trained and experienced genetics service providers as those best qualified to deliver services

Building the Business Case³

- Work Group mission
 - Using the regional networks to develop the information needed to build the case.

Opportunity Knocked

- Cytogenetics and Molecular Cytogenetics
 - One major Medicare payer (WPS) sets an informed policy
 - Two major payers (Noridian and Trailblazer) requested comments on draft LCDs this summer
 - Both were markedly deficient
 - Both are planning more work to sort it out
 - We hope to move them to an ELD
- Genetic counseling

Developing a Defined Network of Genetic Service Providers

- Standards for centers
- Acknowledge qualified providers outside of centers
- Consider specialty genetic condition clinics and core genetic needs
- Include primary care providers identified with the AAP's CSHCN
- Work Group to meet once and then complete work by long distance communication

Issues Complicating Development of National Standards

- Widely variable screening tests and technologies and test cut-offs precludes interstate program comparison
- Patents
 - Development of national evaluation of laboratory performance
 - Directly impacts diagnostic algorithms
- Goals of unifying screen positive case definitions to allow comparison of programs

NCC Projects ²

- Teleconferences
 - Financing
 - Telehealth
 - Carrier Detection
- Technical resources
 - Legal
 - Project related (e.g. telemedicine)

Genetic Counseling Services

- CPT proposal submitted and reviewed favorably
- Genetic counseling practice expense study done and submitted to RUC

NCC Activities

- Annual meeting of regional collaborative group P.I.s
- Newborn screening management guidance for primary care providers
- Telehealth for genetic services

Building the Business Case¹

- Mix of system problems and new technology and knowledge problems
 - System problems amenable to repair
 - CPT
 - RUC
 - ICD
 - SnoMed
 - Outcome studies to support use
 - Trained and experienced genetics service providers as those best qualified to deliver services

Building the Business Case²

- First meeting planned for winter 2005/6
- Work group
 - Maren Scheuner, MD, MPH – Rand Corp.
 - David Ledbetter, PhD – Emory Univ.
 - Rick Carlson, JD – Univ. Washington
 - Debra Doyle, MS – Washington State Dept. Health
 - Marc Williams, MD – IHC
 - Richard Justin – United Health
 - Margretta Seashore, MD – Yale
 - Rick Martin, MD – Washington University
 - James Bartley, MD – Univ. Calif. Irvine
 - Consumer tbn
 - Two others

Developing a Defined Network of Genetic Service Providers

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- Acknowledge qualified providers outside of centers
- Consider specialty genetic condition clinics and core genetic needs
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Management Guidelines

- ACTion Sheets for NBS conditions for primary care providers
- Management guidelines for adults with pediatric genetic diseases
- Management guidelines for medical geneticists

ACT Sheets and Diagnostic Algorithms

- Provide information to facilitate initial responses to screen positive
 - Cover all core and secondary target conditions in NBS panel derived from 31 primary markers
- Point of care education
 - Sent with newborn screening result from NBS labs
- Integrated into AAPs plans for Newborn Screening Clinical Report that updates the AAP Task Force report of 2000.

ACT Sheet – Algorithm Work Group

Metabolic

- Gerard Berry, MD
- Stephen Goodman, MD
- Harvey Levy, MD
- Deborah Marsden, MD
- Dietrich Matern, MD
- William Nyhan, MD, PhD

Primary Care

- Danielle LaRaque, MD
- Barbara Yawn, MD

Newborn Screening Programs

- Kenneth Pass, PhD
- Bradford Therrell, PhD

Project Director

- Michael Watson, PhD

Endocrinology

- Phyllis Speiser, MD
- Stephen LaFranchi, MD

Hematology

- James Eckman, MD
- Carolyn Hoppe, MD
- Peter Lane, MD

Hearing Loss

- Cynthia Morton, PhD
- Richard Smith, MD

Consumer

Kelly Leight, JD

MCHB/HRSA

- Marie Mann, MD
- Michele Lloyd-Puryear, MD, PhD

Newborn Screening Act Sheet (1.18.06 FINAL draft) [FS]

Sickle Cell Anemia (HbSS Disease or HbS/beta zero thalassemia)

Condition Description- A red blood cell disorder characterized by presence of fetal hemoglobin (F) and hemoglobin S in the absence of hemoglobin A. The hemoglobins are listed in order of the amount of hemoglobin present (F>S). This result is different from FAS which is consistent with sickle carrier.

Differential Diagnosis – Homozygous sickle cell disease (Hb SS), sickle beta-zero thalassemia, or sickle hereditary persistence of fetal hemoglobin (S-HPFH).

You Should Take the Following Actions:

- Contact the family to inform them of the screening result.
- Consult a specialist in hemoglobinopathies; refer if needed.
- Evaluate infant and assess for splenomegaly.
- Initiate timely confirmatory/diagnostic testing as recommended by consultant.
- Initiate daily penicillin VK (125mg po bid) prophylaxis and other treatment as recommended by the consultant.
- Educate parents/caregivers regarding the risk of sepsis, the need for urgent evaluation for fever of $\geq 38.5^{\circ}\text{C}$ (101°F) and signs and symptoms of splenic sequestration.

Diagnostic Evaluation – Hemoglobin separation by electrophoresis, isoelectric focusing or HPLC showing FS pattern. Family or DNA studies may be used to confirm genotype. Sickledex is not appropriate for confirmation in newborns and infants.

Clinical Considerations – Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood. Complications include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crisis, dactylitis, priapism and stroke. Comprehensive care including family education, immunizations, prophylactic penicillin and prompt treatment of acute illness reduces morbidity and mortality. S-HPFH is typically benign.

Additional Information –

Grady Comprehensive Sickle Cell Center Web Site: <http://www.scinfo.org/newborn>

Management and Therapy of Sickle Cell Disease

<http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm>

Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for Comprehensive Care, and Protocols for Management of Acute and Chronic Complications.

http://www.tdh.state.tx.us/newborn/sc_guide.htm

American Academy of Pediatrics <http://pediatrics.aappublications.org/cgi/content/full/109/3/526>

Sickle Cell Disease Association <http://www.sicklecelldisease.org>

Disclaimer: These standards and guidelines are designed primarily as an educational resource for physicians to help them provide quality medical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the clinical laboratory hematologist or molecular geneticist should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the laboratory record the rationale for any significant deviation from these standards and guidelines.

FS

- ***Condition Description-*** A red blood cell disorder characterized by presence of fetal hemoglobin (F) and hemoglobin S in the absence of hemoglobin A. The hemoglobins are listed in order of the amount of hemoglobin present (F>S). This result is different from FAS which is consistent with sickle carrier.
-
- ***Differential Diagnosis*** – Homozygous sickle cell disease (Hb SS), sickle beta-zero thalassemia, or sickle hereditary persistence of fetal hemoglobin (S-HPFH).

FS Act Sheet

You Should take the Following Actions

- Contact the family to inform them of the screening result.
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- Evaluate infant and assess for splenomegaly.
- Initiate timely confirmatory/diagnostic testing as recommended by consultant.
- Initiate daily penicillin VK (125mg po bid) prophylaxis and other treatment as recommended by the consultant.
- Educate parents/caregivers regarding the risk of sepsis, the need for urgent evaluation for fever of $\geq 38.5^{\circ}\text{C}$ (101°F) and signs and symptoms of splenic sequestration.
- Report findings to state newborn screening program.

FS Act Sheet

- ***Diagnostic Evaluation*** – Hemoglobin separation by electrophoresis, isoelectric focusing or HPLC showing FS pattern. Family or DNA studies may be used to confirm genotype. Sickledex is not appropriate for confirmation in newborns and infants.
- ***Clinical Considerations*** – Newborn infants are usually well. Hemolytic anemia and vaso-occlusive complications develop during infancy or early childhood. Complications include life-threatening infection, splenic sequestration, pneumonia, acute chest syndrome, pain episodes, aplastic crisis, dactylitis, priapism and stroke. Comprehensive care including family education, immunizations, prophylactic penicillin and prompt treatment of acute illness reduces morbidity and mortality. S-HPFH is typically benign.

FS Act Sheet

- ***Additional Information –***
- **Grady Comprehensive Sickle Cell Center Web Site:**
<http://www.scinfo.org/newborn>
- **Management and Therapy of Sickle Cell Disease**
<http://www.nhlbi.nih.gov/health/prof/blood/sickle/index.htm>
- **Sickle Cell Disease in Children and Adolescents: Diagnosis, Guidelines for Comprehensive Care, and Protocols for Management of Acute and Chronic Complications.**
http://www.tdh.state.tx.us/newborn/sc_guide.htm
- **American Academy of Pediatrics**
<http://pediatrics.aappublications.org/cgi/content/full/109/3/526>
- **Sickle Cell Disease Association** <http://www.sicklecelldisease.org>

FS Act Sheet - page 2

- ***Resources for Referral*** – *Insert local, state, regional and national resources*
- <http://www.rhofed.com/sickle/index.htm>
- <http://scinfo.org/newborn>
- ***Local Resources:*** Insert state newborn screening program web site

Newborn Screening ACT Sheet (1.18.06 FINAL draft)
Fatty Acid Oxidation Disorder (FAOD)
[Elevated C8 with lesser elevations of C6 and C10 acylcarnitine]
Medium-chain acyl-CoA dehydrogenase (MCAD def.)

Differential Diagnosis: Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

Condition Description: MCAD deficiency is a fatty acid oxidation disorder (FAOD). Fatty acid oxidation occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In an FAOD, fatty acids and potentially toxic derivatives accumulate because of a deficiency in one of the mitochondrial FAO enzymes.

MEDICAL EMERGENCY - TAKE THE FOLLOWING IMMEDIATE ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, lethargy, hypotonia, hepatomegaly). If signs are present or infant is ill, initiate emergency treatment with IV glucose. Transport to hospital for further treatment in consultation with metabolic specialist. If infant is normal initiate timely confirmatory/diagnostic testing, as recommended by specialist.
- Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.
- Report findings to newborn screening program.

Diagnostic Evaluation: Plasma acylcarnitine analysis will show elevated **octanoylcarnitine (C8)**. Urine acylglycine will show elevated **hexanoylglycine**. Diagnosis is confirmed by mutation analysis of the **MCAD gene**.

Clinical Considerations: MCAD deficiency is usually asymptomatic in the newborn although it can present acutely in the neonate with hypoglycemia, metabolic acidosis, hyperammonemia, and hepatomegaly. MCAD deficiency is associated with high mortality unless treated promptly; milder variants exist. Hallmark features include vomiting, lethargy, and hypoketotic hypoglycemia. It is a significant cause of sudden death.

Additional Information:

Emergency Treatment Protocol

(<http://www.childrenshospital.org/newenglandconsortium/>)

[MCAD Emergency Protocol](#)

Gene Tests (<http://www.genetests.org/>)

[Testing for MCAD deficiency](#)

OMIM (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>)

[MCAD deficiency](#)

Genetics Home Reference (<http://ghr.nlm.nih.gov/>)

[MCAD deficiency](#)

Elevated C8 with lesser elevations of C6 and C10 acylcarnitine

- ***Differential Diagnosis:*** Medium-chain acyl-CoA dehydrogenase ([MCAD](#)) deficiency
- ***Condition Description:*** MCAD deficiency is a fatty acid oxidation disorder (FAOD). Fatty acid oxidation occurs during prolonged fasting and/or periods of increased energy demands (fever, stress) when energy production relies increasingly on fat metabolism. In an FAOD, fatty acids and potentially toxic derivatives accumulate because of a deficiency in one of the mitochondrial FAO enzymes.

Elevated C8 with lesser elevations of C6 and C10 acylcarnitine

- ***MEDICAL EMERGENCY - TAKE THE FOLLOWING IMMEDIATE ACTIONS:***
- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, lethargy, hypotonia, hepatomegaly). If signs are present or infant is ill, initiate emergency treatment with IV glucose. Transport to hospital for further treatment in consultation with metabolic specialist. If infant is normal initiate timely confirmatory/diagnostic testing, as recommended by specialist.
- Educate family about need for infant to avoid fasting. Even if mildly ill, immediate treatment with IV glucose is needed.
- Report findings to newborn screening program.

Elevated C8 with lesser elevations of C6 and C10 acylcarnitine

- **Diagnostic Evaluation:** Plasma acylcarnitine analysis will show elevated **octanoylcarnitine (C8)**. Urine acylglycine will show elevated **hexanoylglycine**. Diagnosis is confirmed by mutation analysis of the **MCAD gene**.
-
- **Clinical Considerations:** MCAD deficiency is usually asymptomatic in the newborn although it can present acutely in the neonate with hypoglycemia, metabolic acidosis, hyperammonemia, and hepatomegaly. MCAD deficiency is associated with high mortality unless treated promptly; milder variants exist. Hallmark features include vomiting, lethargy, and hypoketotic hypoglycemia. It is a significant cause of sudden death.

Elevated C8 with lesser elevations of C6 and C10 acylcarnitine

Additional Information:

- **Emergency Treatment Protocol**
- (<http://www.childrenshospital.org/newenglandconsortium/>) [MCAD Emergency Protocol](#)
- **Gene Tests** (<http://www.genetests.org/>)
[Testing for MCAD deficiency](#)
- **OMIM**
(<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>) [MCAD deficiency](#)
- **Genetics Home Reference**
(<http://ghr.nlm.nih.gov/>) [MCAD deficiency](#)

Newborn Screening ACT Sheet (1.18.06 FINAL draft) [Elevated C16 and/or C18:1 acylcarnitine] Carnitine acylcarnitine transporter defect

Differential Diagnosis: Carnitine/acylcarnitine transporter (CACT); CPT2 deficiency

Condition Description: In both the translocase and CPT2 deficiencies, the acylcarnitines cannot be transported into the mitochondria for fatty acid oxidation. Thus, the need for generation of energy from fatty acids during fasting or increased demand (fever, stress) cannot be met. In addition, the neonatal form of CPT2 deficiency is associated with multiple congenital anomalies.

Take the Following IMMEDIATE Actions:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- See and evaluate infant (hepatomegaly, cardiac insufficiency; history of sudden unexpected death in a sibling; dysmorphic facies).
- Consultation/referral to a metabolic center to determine appropriate follow-up.
- Emergency treatment if symptomatic hand/or hypoglycemia present.
- Report findings to newborn screening program.

Confirmation of Diagnosis: Plasma acylcarnitine analysis reveals increased C16 and/or C18:1. Urine organic acid analysis reveals increased lactic acid and dicarboxylic acids.

Clinical Considerations: In the neonatal form of CPT2 deficiency, the neonate is profoundly ill with marked hypoglycemia, metabolic acidosis, cardiac arrhythmias, and facial dysmorphism. Only rarely will these infants survive. In the later-onset muscular form of CPT2 deficiency, the neonate is asymptomatic but muscle disease develops in the adolescent or adult years. Translocase deficiency presents similarly to the neonatal form of CPT2 deficiency.

Additional Information:

Emergency Treatment Protocol

<http://www.childrenshospital.org/newenglandconsortium/>

Gene Tests (<http://www.genetests.org/>)

PubMed (<http://www.ncbi.nlm.nih.gov/entrez/>)

OMIM (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>)

Genetics Home Reference (<http://ghr.nlm.nih.gov/>)

[LCHAD/TFP Emergency Protocol](#)

[Testing for LCHAD/TFP deficiency](#)

[LCHAD & TFP deficiency](#)

[LCHAD & TFP deficiency](#)

[LCHAD & TFP deficiency](#)

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Referral (Local, state, regional and national ([Search for Metabolic Specialist](#))):

Testing: <http://biochemgen.ucsd.edu/UCSDW3BG/Labchoose.asp>

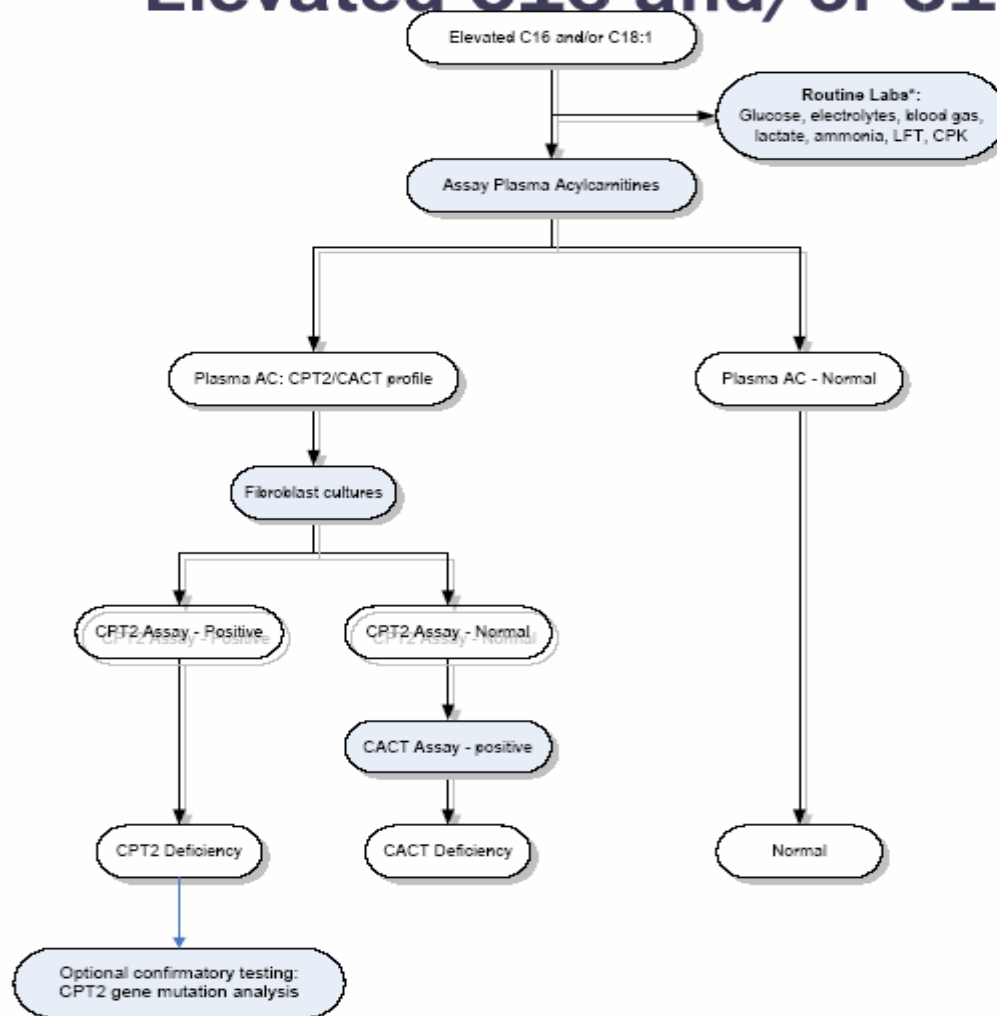
Clinical: <http://www.genetests.org/servlet/access?id=8888891&key=RRqZcXXEUiAx9&fcn=y&fw=zLsf&filename=/clinicsearch/searchclinic.html>

Local Resources: Insert state newborn screening program web site

Diagnostic Algorithms

- Descriptive follow-up algorithm
 - requested by clinical and biochemical geneticists
 - included with primary care provider materials
- Initiation point for routine diagnostics depends on predictive value of screening test

Elevated C16 and/or C18:1 (2.1.0)



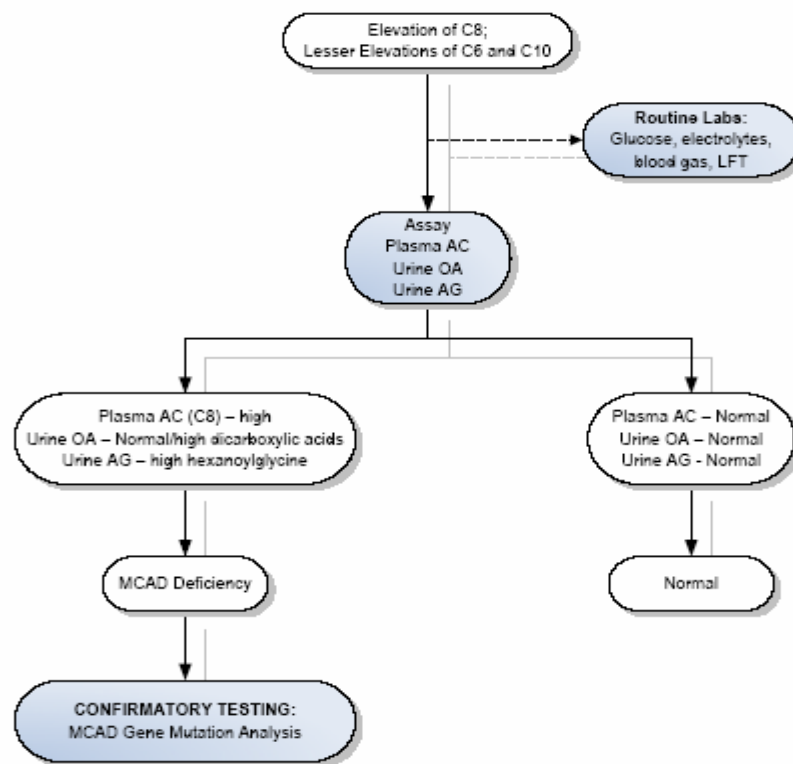
Abbreviations and footnotes:

LFT – liver function test
 CPK – creatine phosphokinase
 AC - acylcarnitine
 CPT2 – carnitine palmitoyl transferase 2
 CACT – carnitine acylcarnitine translocase

* Timing of associated diagnostic testing varies with predictive value of screening test

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Elevation of C8 with Lesser Elevations of C6 and C10 (2)

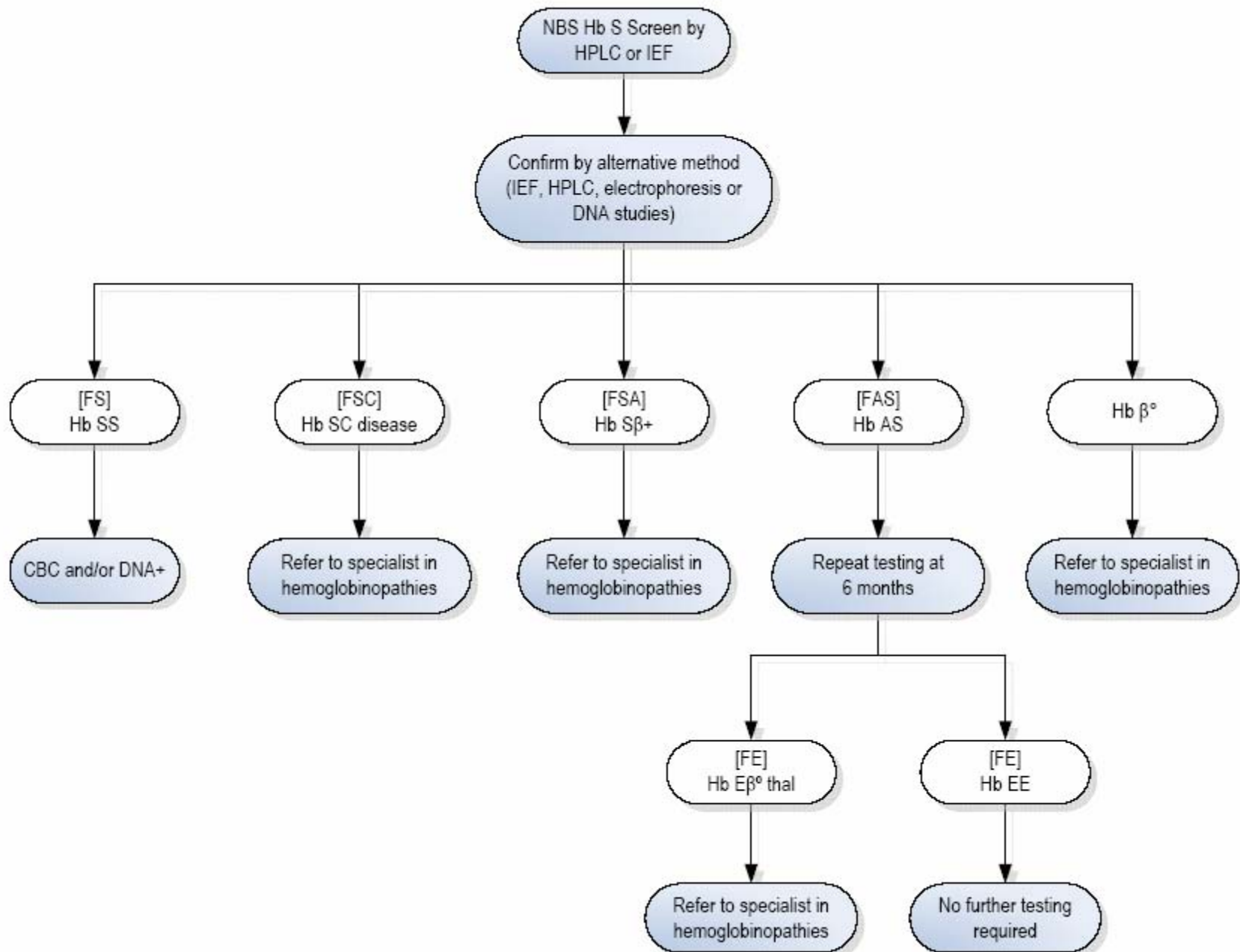


Abbreviations

LFT – liver function tests
 MCAD – Medium-chain acyl-CoA dehydrogenase
 AC – acylcarnitine
 OA – organic acid
 AG – acylglycine

These standards and guidelines are designed primarily as an educational resource for physicians to help them provide quality clinical services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the health care provider should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the laboratory record the rationale for any significant deviation from these standards and guidelines.

Hb S Screening (1.25.06)



Related Projects

- ACT sheets based on genetic tests offered outside of NBS
 - Point-of-care applications in education and response guidance
 - Based on indications
 - Follow formal development of guidelines
 - Utilize network of US laboratories