Nomination Process for Candidate Conditions on the Uniform Screening Panel

A Trial Run of a Condition Using the Proposed Nomination Process

7th Meeting of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC)

February 14th 2006
NEWBORN SCREENING:
TOWARD A UNIFORM SCREENING PANEL
AND SYSTEM

http://mchb.hrsa.gov/screening/
Impact of Uniform Panel

30% of US births

66%

30%

4%

4%
Impact of Uniform Panel

2004

37% of US births

No. of states

No. of conditions

18%
17%
35%
20%
Impact of Uniform Panel

- 20% of US births (2006)
- 63% of US births
- 14% of US births

% of US births

- <5
- 5-10
- 11-20
- 21-30
- >30

No. of conditions

- 66%

No. of states
Proponent

Nomination of condition

Submission of nomination to HRSA (forms)

HRSA

Nomination DECLINED to be reviewed by ACHDGDNC

Administrative APPROVAL to be reviewed by ACHDGDNC

ACHDGDNC

Committee APPROVAL to be reviewed by subcommittees

ACHDGDNC subcommittees

Recommendation NOT to form ad hoc working group (AHWG)

Recommendation to ACHDGDNC to form ad hoc working group

ACHDGDNC

Nomination DECLINED to be reviewed by subcommittees

Recommendation to form AHWG

Recommendation NOT to include condition in uniform panel

ACHDGDNC recommendation for INCLUSION of condition in uniform panel

Ad hoc working group

AHWG formed inclusive of liaisons of the three subcommittees

Report and presentation to ACHDGDNC

ACHDGDNC recommendation for INCLUSION of condition in uniform panel

UNIFORM PANEL

Nomination DECLINED to be reviewed by ACHDGDNC

Nomination DECLINED to be reviewed by subcommittees

ACHDGDNC recommendation NOT to include condition in uniform panel

End
Examples of Candidate Conditions for Expansion of Uniform Panel (in alphabetical order)

- CDG type Ib
- CMV
- DMD
- G6PD
- Fabry disease
- FHC
- HIV
- Krabbe disease
- Pompe disease
- SCID
- SMA
- Toxoplasmosis
- Wilson disease
- Many (?) others……
Nomination Process

- **Who**
- **What**
- **When**

Nomination of condition

Proponent

Submission of nomination to HRSA (forms)

HRSA
Nomination Process

• Who

• What

• When

Nomination of condition

Proponent

Submission of nomination to HRSA (forms)

HRSA
Requirement for Nominating a Condition for Addition to the Uniform Panel

• Cover letter (from proponent)

• Nomination form (NF)

• References (up to 15, listed on NF)
**Condition**

**Screening Test**

**Treatment**

**References**
### Format Similar to Fact Sheets

**CONDITION**

| Type of Disorder | Medium-chain acyl-CoA dehydrogenase deficiency (MCAD deficiency) |

**ETHNICITY**

- Inborn error of metabolism, fatty acid oxidation disorder
- Predominantly Caucasians, Northern European ancestry, less frequent in Hispanics, rare in African-Americans, very rare in Orientals

**SCREENING METHOD(S)**

- Tandem mass spectrometry (MS/MS)
- Screened for in 31 of 51 states, 58% of annual births (as of August 2004)

**SURVEY SCORES**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Consensus</th>
<th>% of max score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>&gt;1,25,000</td>
<td>75%</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Almost never</td>
<td>91%</td>
</tr>
<tr>
<td>Sudden unexplained death</td>
<td>Profound</td>
<td>84%</td>
</tr>
</tbody>
</table>

**The test**

- Screening test: Yes (MS/MS) 100%
- Available in CBS or by physical method: Yes 99%
- High throughput: Yes 92%
- Overall cost: <$1 (Yes, lack of consensus) 59%
- Multiple analytes: Yes 92%
- Secondary targets: Yes 74%
- Multiplex platform: Yes 70%

**The treatment**

- Availability & cost: Widely available 94%
- Efficacy of treatment: Potential to prevent ALL negative consequences 82%
- Benefits of early intervention: Early intervention optimizes individual outcome 90%
- Benefits of early identification: Early identification benefits family & society 94%
- Prevention of mortality: Yes 92%
- Confirmation of diagnosis: Limited availability (lack of consensus) 71%
- Acute management: Limited availability 70%
- Simplicity of therapy: Periodic involvement of specialist 77%

**REFERENCES AND WEB SITES**


**INCLUSION CRITERIA**

<table>
<thead>
<tr>
<th>Test available</th>
<th>YES</th>
<th>Type</th>
<th>MS/MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z score of higher scoring condition?</td>
<td>1.36</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Final score</td>
<td>1.98</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td>% of max score</td>
<td>84%</td>
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</table>

**ASSESSMENT**

- Primary target, inclusion in uniform panel: YES

**COMMENT**

- MCAD deficiency had the highest score on the panels of conditions included in this study. This condition meets the criteria for inclusion in the uniform panel and state programs currently not sequencing for MCAD deficiency should strongly encourage to add this condition to their panel as soon as feasible. Differential diagnosis of secondary targets needs to be considered. Regionalization of analytical services has been adopted already in a few regions.

- No special food or orphan drug required 50%.

**REFERENCES AND WEB SITES**

MCAD Deficiency

HRSA/ACMG UNIFORM PANEL (DRAFT 01/23/06)

NOMINATION OF CONDITION - Fact Sheet

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medium-chain 3-ket-0-CoA dehydrogenase (MCAD) deficiency</th>
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<tbody>
<tr>
<td>Type of disorder</td>
<td>Fatal acidosis disorder</td>
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<tr>
<td>Screening method</td>
<td>Tandem mass spectrometry (TMS)</td>
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<tr>
<td>Treatment strategy</td>
<td>Avoidance of fasting (testing feeding), low fat diet, carnitine supplementation</td>
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</table>

**Incidence**
- Reference required. In pediatric screening or clinical identification, MCAD deficiency is currently screened in 18% of US newborns (1:6,600). The incidence is between 1:10,000 and 1:20,000 live births, highest prevalence among Northern European ancestry. A single mutation (G93A=D) accounts for approximately 50% of mutant alleles with a carrier frequency of 1.4%. Hispanic and Asian "common" mutations have been described, but the overall incidence is lower.

**Timing of clinical onset**
- (Reference of the timing of newborn screening to detect clinical manifestations) - Screening at birth could prevent severe metabolic decompensation and sudden unexpected death in exclusively breast-fed newborns. However, these events occur more frequently in the first 72 hours of life, at a time when a diagnosis may not yet be available. First onset of symptoms is often after several months or years (see severity below).

**Severity of disease**
- (Mobidity, disability, mortality) - Up to 50% of patients with MCAD deficiency due to a consequence of the first acute episode of fasting intolerance and metabolic decompensation. A strong association with sudden unexpected death in early life has been documented. Survival may be associated with persistent neurologic damage that requires lifetime care and drug treatment.

**Test**

| Screening test(s) to be used | High volume method, platform | Tandem mass spectrometry, allylamine (4-ethyl) profiling by parent on analysis (E6). Informative markers include C8, C8 (primary), C10, C10.2, C12.2, C10. A typical MCAD profile shows elevation of all these species with a characteristic pattern (C8: C8+1; C10: C10+1; C10: C10 ratio > 5) but different patterns could be detected. Carriers are detectable biochemically (C8:C10:C12 pattern) |

**Modality of screening**
- (Detection, duration, site, preliminary results of testing pilot study for clinical validation) - Tandem mass spectrometry is the preferred method. Detection of the G93A=D mutation and sequencing of the entire gene is also possible, however, additional specimens are collected.

**Clinical validation**
- (Sensitivity, specificity, detection rate, positive predictive value, false positive rate) - In 2006, the MN program detected 37 cases with an elevated C8 at the first screening (N=1,677). Ten of them were rejected as abnormal. Four were confirmed to be affected. Three of the other six were heterozygotes. The performance metrics were as follows: sensitivity, 100%; specificity, 99.98%; detection rate, 1:17,964; positive predictive value 99.98%; false positive rate, 0.0008%.

**Laboratory performance metrics**
- (Reliability, availability) - Confirmatory testing is relatively available and based on plasma allylamine analysis and urine acylcarnitine analysis. These tests are highly reliable when properly interpreted. The diagnostic markers are the same acylcarnitine species detected by newborn screening (C8, C8+1; C10, C10.2; C10.2). Analytes are stable in plasma, urine, and blood drawn at the time of diagnosis.

**Confirmatory testing**
- (False positives, cause of misdiagnosis, method of detection) - Analytes can be detected, however, it is critical to be properly identified by pattern recognition. Collection of blood spots is a routine form of blood drawing and implies minimal risk.

**Risks**
- (Potentially medical or other ill effects or harms from testing) - Clinical testing and high-dose intake could lead to excessive weight gain. Regular monitoring by a nutritionist or dietitian is essential for good outcomes.

**Nomination of condition (page 2)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene</th>
<th>ACMG</th>
<th>Legacy</th>
<th>SpID</th>
<th>OMIM</th>
<th>201460</th>
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</table>

**Treatment**
- (Drug(s), diet, replacement therapy, transplant, other) - The cornerstone of treatment is fasting avoidance and frequent feeding in early life. Cautionary measures at the time of intercurrent illness (hospitalisation and IV fluids) are very effective in preventing acute metabolic decompensation. Carnitine supplementation is regarded by some investigators to be beneficial.

**Urgency**
- (How soon after birth treatment needs to be initiated to be effective) - Frequent feeding of an affected newborn should be implemented as soon as possible.

**Efficacy**
- (Extent of prevention of mortality, morbidity, disability) - With few anecdotal exceptions, patients diagnosed by NBS are likely to have a substantial reduction and often elimination of acute episodes of decompensation.

**Availability**
- (Any limits of availability) - Treatment is based on changes of dietary habit and is widely available, and therefore effective.

**References**

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</table>
Nomination Form

• Condition

• Test

• Treatment
Incidence

(Reference required; By pilot screening or clinical identification?)

MCAD deficiency is currently screened in xx% of US newborns (xx/51 states). The NBS-based incidence is between 1:10-20,000 live births, higher if predominant Northern European ancestry. A single mutation (985A>G) accounts for approximately 60% of mutant alleles with a carrier frequency of 1:40. Rare in African-Americans. Hispanic and Asian "common" mutations have been described, but the overall incidence is lower.
Timing of Clinical Onset
(Relevance of the timing of newborn screening to onset of clinical manifestations)

Screening at birth could prevent severe metabolic decompensation and sudden unexpected death in exclusively breast-fed newborns. However, these events occur more frequently in the first 72 hours of life, at a time when screening results may not be available yet. First onset of symptoms is frequently at several months, or years, of age.
30-50% of patients with MCAD deficiency die as a consequence of their first acute episode of fasting intolerance and metabolic decompensation.

A strong association with sudden unexpected death in early life has been documented.

Survival may be associated with permanent neurological damage and significant disability requiring lifetime care and drug treatment.
Nomination Form

• Condition

• Test

• Treatment
Screening Test(s) To Be Used

MS/MS is a high throughput platform (>500 tests/unit/day).

Precursor ion scan of m/z 85 for acylcarnitine profiling.

Informative markers are C8 (primary), C6, C10:1, and C10.

The following ratios are also useful: C8/C2, C8/C10.

A typical MCAD profile shows elevation of these markers with a characteristic pattern (C6<C8>C10; C10:1>C10, C8/C10 ratio >5) but different patterns could be detected. Carriers may be detected (C6<C8<C10).
Normal profile
Modality of Screening

(Dried blood spot, physical or physiologic assessment, other)

Biochemical analysis of dried blood spots is the preferred method.

Detection of the 985A>G mutation and sequencing of the entire gene is also possible without the collection of additional specimens.
Clinical Validation

(Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation)

Newborn screening for MCAD deficiency has been validated multiple times by several state programs in the US and worldwide, all leading to the same conclusion that it is appropriate to screen for this disorder.

In the HRSA/ACMG survey (2002-2004) MCAD was the highest scoring condition among 81 considered.
Laboratory Performance Metrics
(Sensitivity, specificity, detection rate, positive predictive value, false positive rate)

In 2005, the MN program detected 37 cases with an initial C8 value above cutoff (N=71,677). Ten of them were reported as abnormal, four were confirmed to be affected, three of the other six were heterozygotes by genotyping.

The performance metrics were as follows: sensitivity: 100%; specificity 99.99%; detection rate: 1:17,994; positive predictive value: 40%; false positive rate: 0.008%
Confirmatory testing is relatively available and is based on plasma acylcarnitine analysis and urine acylglycine analysis. These tests are reliable when properly interpreted. The diagnostic markers are the same AC species detected by newborn screening (C6, C8, C10:1, C10, and ratios) in plasma, hexanoylglycine and suberylglucine in urine. Plasma carnitine and urine organic acids are NOT reliable in asymptomatic patients. Sequencing of the entire gene is required in patients with only one, or none, 985A>G allele.
Risks
(False positives, carrier detection, invasiveness of method, other)

Analysis in MRM mode could not detect drug artifacts (m/z 342 and m/z 366) which are very common in premature newborns. Full scan acquisition mode and adequate post-analytical interpretive skills should prevent reporting of unnecessary false positive results.
Risks

(False positives, carrier detection, invasiveness of method, other)

Carriers may be detected by screening and should not be reported. Exceptions could be considered in specific cases (family history of sudden death).

Genotyping of an affected case could lead to disclosure of non-paternity.

Collection of blood spots is a routine form of blood drawing and implies minimal risk.
Nomination Form

• Condition

• Test

• Treatment
The cornerstones of treatment are fasting avoidance and frequent feedings in early life. Cautionary measures at the time of intercurrent illness (hospitalization and IV fluids) are very effective in preventing acute metabolic decompensation. Carnitine supplementation is regarded by some investigators to be beneficial.
Urgency
(How soon after birth treatment needs to be initiated to be effective)

Frequent feeding of an affected newborn should be implemented as soon as possible to minimize the risk of acute illness
Efficacy
(How soon after birth treatment needs to be initiated to be effective)

Frequent feeding of an affected newborn should be implemented as soon as possible to minimize the risk of a fasting intolerance event due to inadequate feeding, infections and other environmental stressors.
Availability
(Any limits of availability)

Treatment is based on changes of dietary habits and is widely available and affordable.

Carnitine may not be covered by some insurers.
Risks
(Potential medical or other ill effects from treatment)

Frequent feedings and high caloric intake could lead to excessive weight gain.

Regular monitoring by a nutritionist or dietician is essential for good outcome.
Ladies and gentlemen, please start your engines...