Nomination Process for Candidate Conditions on the Uniform Screening Panel

A Trial Run of a Condition Using the Proposed Nomination Process

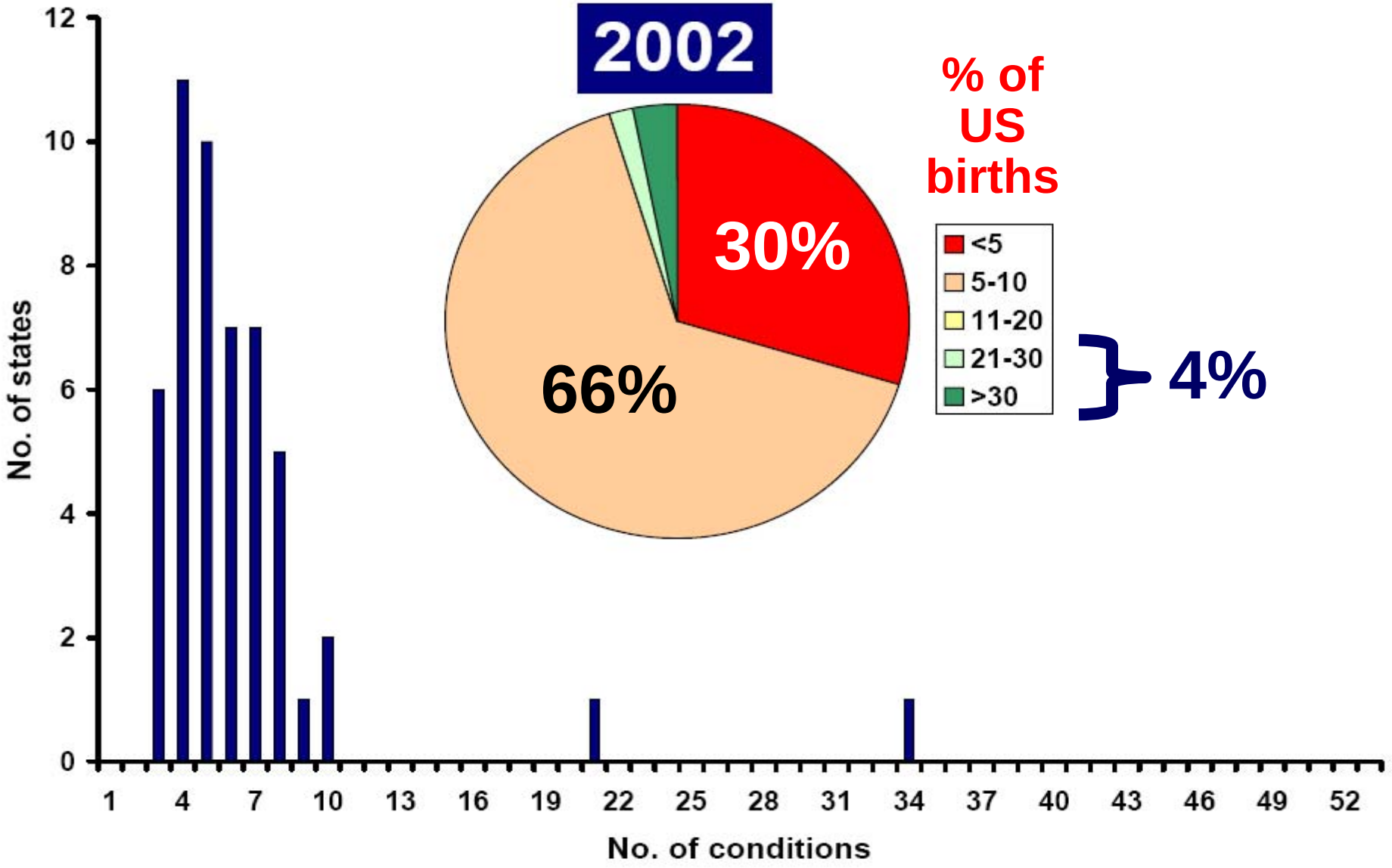
7th Meeting of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC)

February 14th 2006

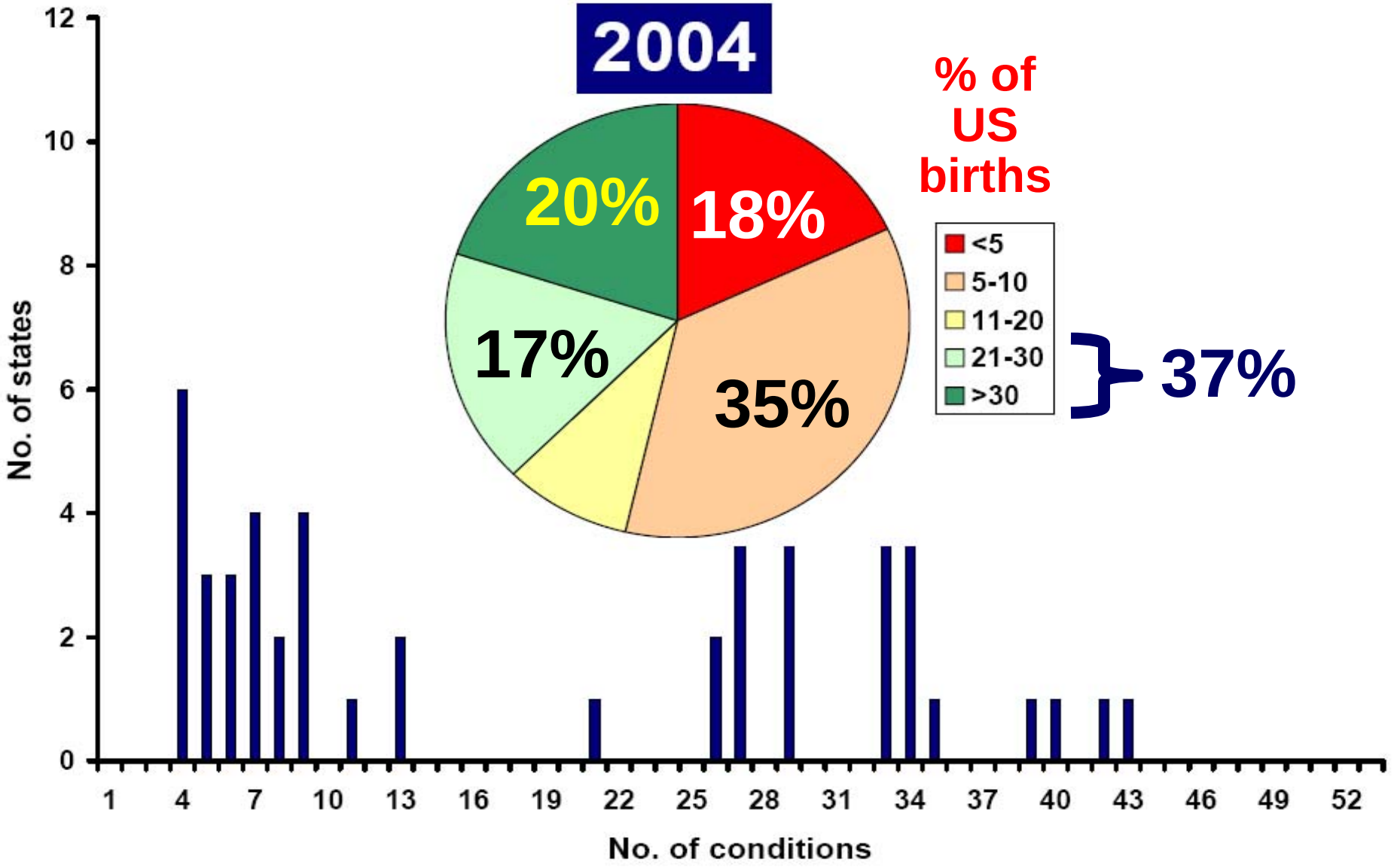
NEWBORN SCREENING: TOWARD A UNIFORM SCREENING PANEL AND SYSTEM

http://mchb.hrsa.gov/screening/

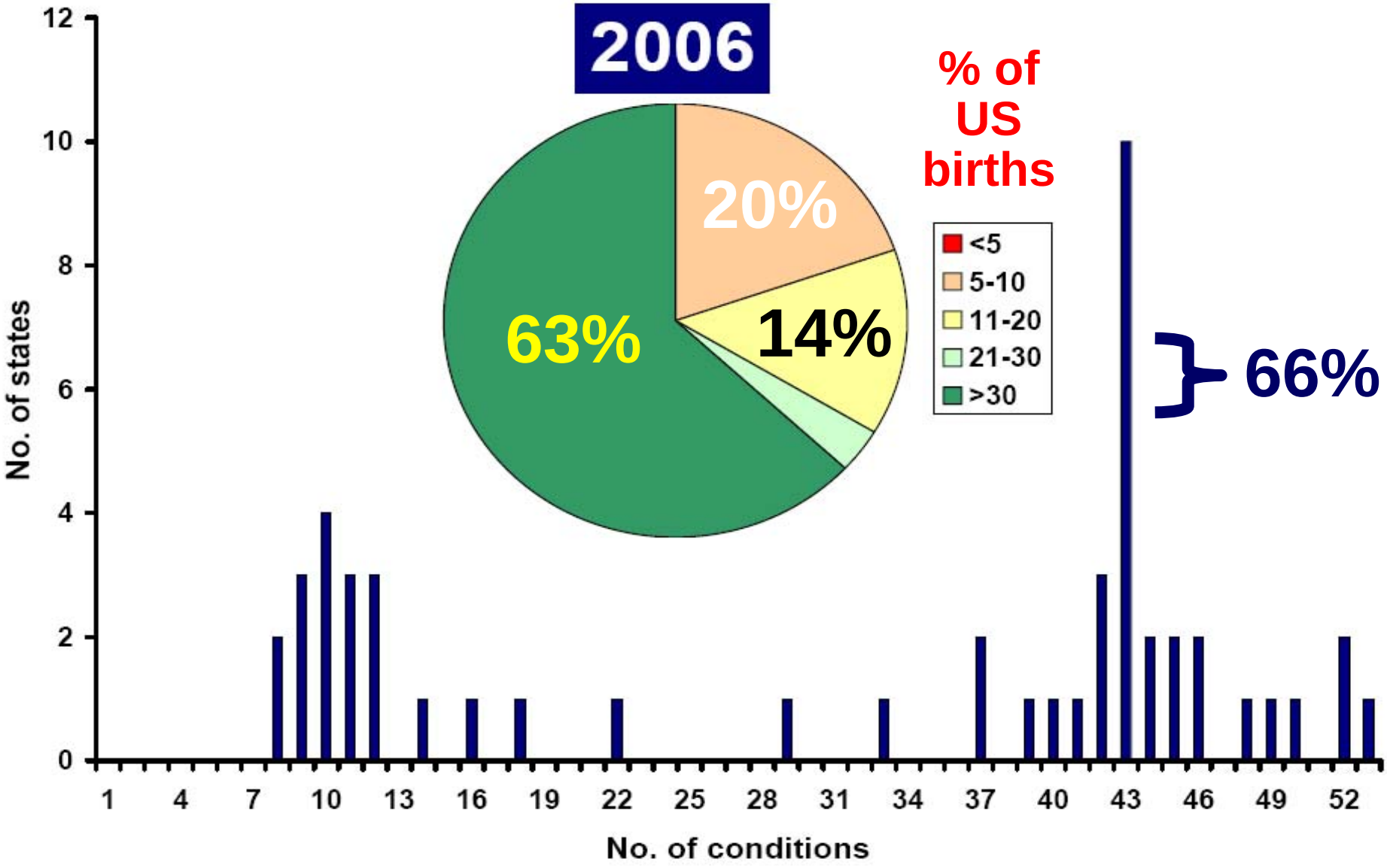
Impact of Uniform Panel

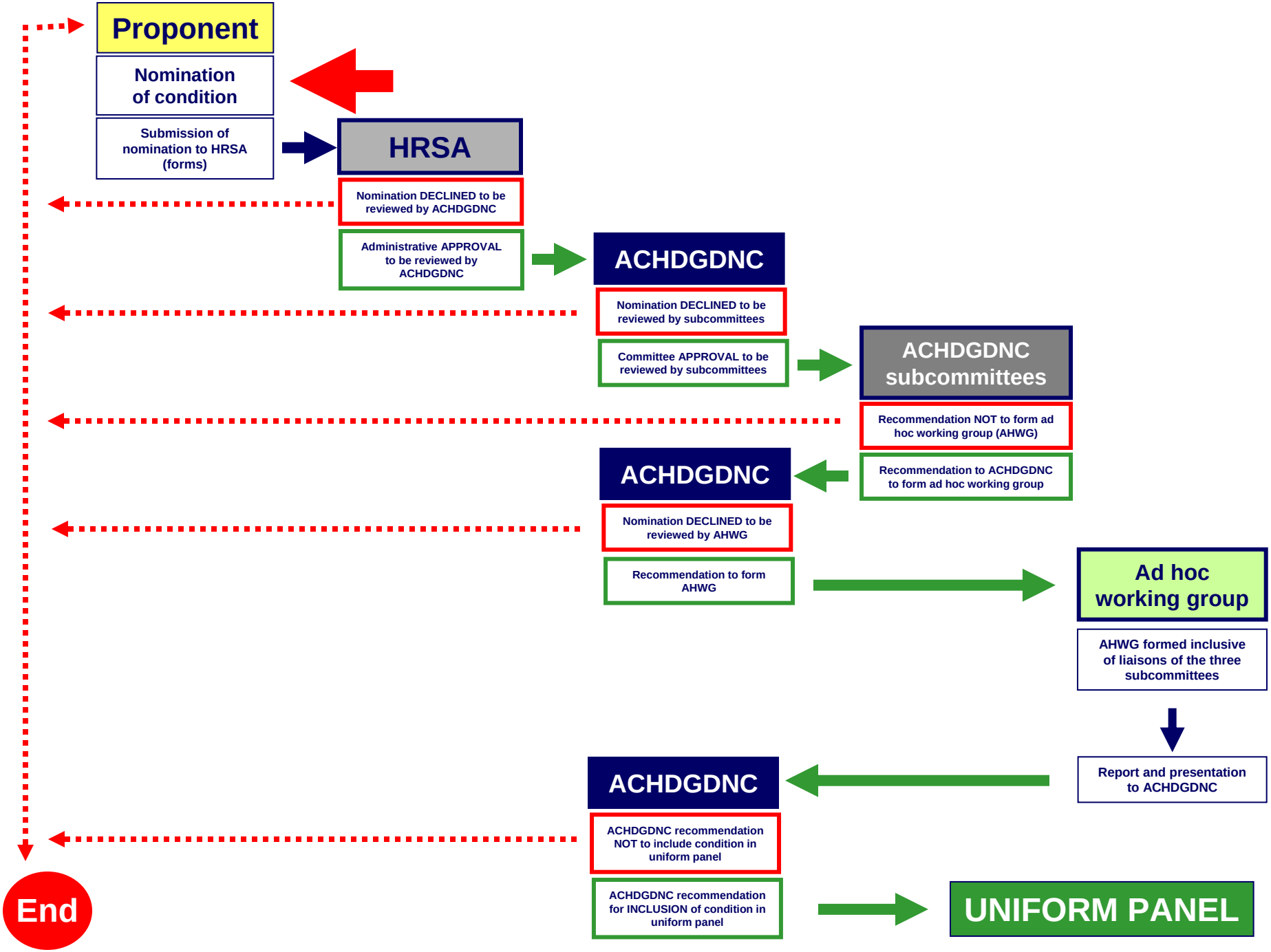


Impact of Uniform Panel



Impact of Uniform Panel



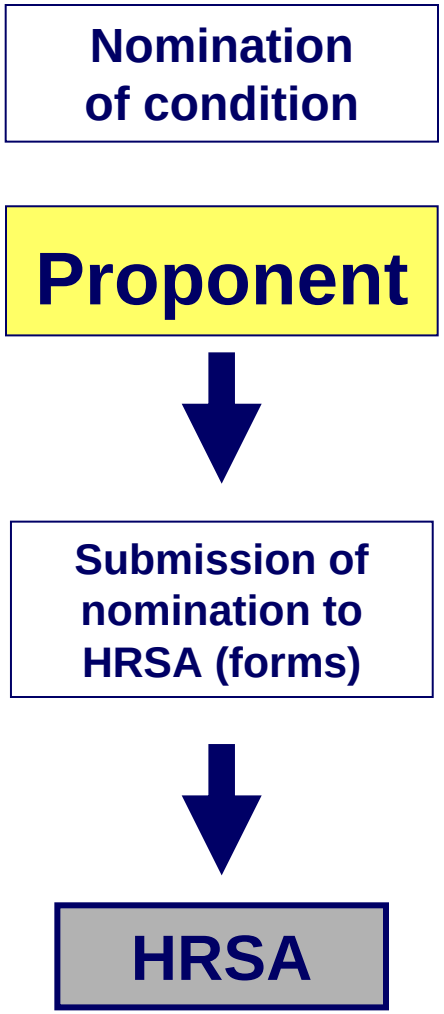

Proponent
Nomination of condition
Submission of nomination to HRSA (forms)
HRSA
Nomination DECLINED to be reviewed by ACHDGDNC
Administrative APPROVAL to be reviewed by ACHDGDNC
ACHDGDNC
Nomination DECLINED to be reviewed by subcommittees
Committee APPROVAL to be reviewed by subcommittees
ACHDGDNC subcommittees
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 AHWG
Recommendation to form AHWG
Ad hoc working group
AHWG formed inclusive of liaisons of the three subcommittees
Report and presentation to ACHDGDNC
ACHDGDNC
ACHDGDNC recommendation NOT to include condition in uniform panel
ACHDGDNC recommendation for INCLUSION of condition in uniform panel
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……

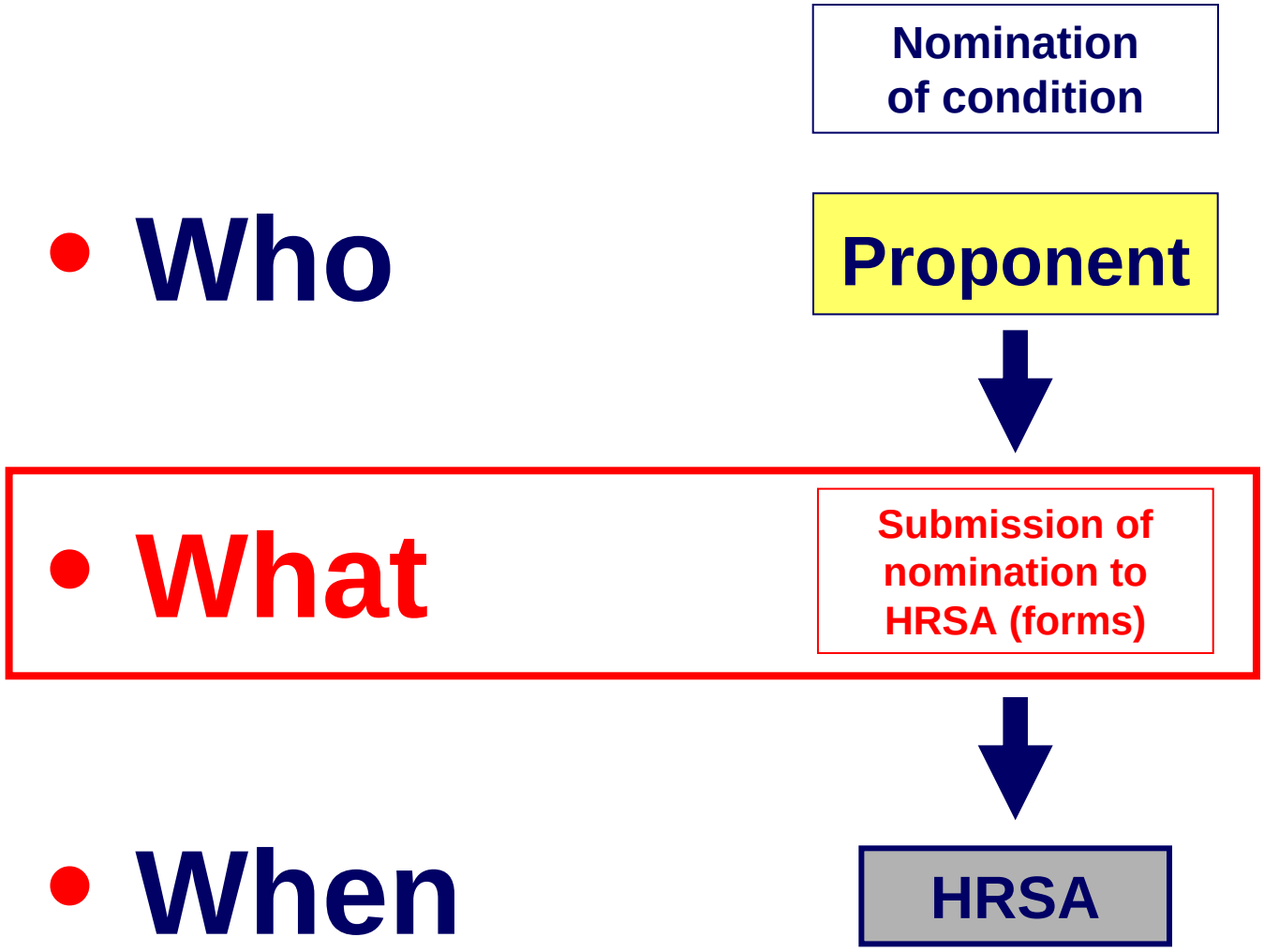
Nomination Process

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



Nomination Process

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



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)

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

NOMINATION OF CONDITION - Fact Sheet

Name of proponent		Date	
Condition			
Type of disorder			
Screening method			
Treatment strategy			

CONDITION	Comment	Gene		Locus		OMIM	
Incidence	(Reference required; By pilot screening or clinical identification?)						
Timing of clinical onset	(Relevance of the						
Severity of disease	(Morbidity, disability, mortality)						

TEST	Comment
Screening test(s) to be used	(High volume method, platform)
Modality of screening	(Dried blood spot, physical or physiologic assessment, other)
Clinical validation	(Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation)
Laboratory performance metrics	(Sensitivity, spe
Confirmatory testing	(Reliability, avai
Risks	(False positives, carrier detection, invasiveness of method, other)

Condition

Screening Test

Nomination of condition (page 2)

TREATMENT	Comment
Modality	(Drug(s), diet, replacement therapy, transplant, other)
Urgency	(How soon after birth treatment needs to be initiated to be effective)
Efficacy	(Extent of preve
Availability	(Any limits of availability)
Risks	(Potential medical or other ill effects from treatment)

Treatment

KEY REFERENCES (Specific citations - limit to 15)	
1	
2	
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11	

Submit nomination to:

Michele A. Lloyd-Puryear, M.D., Ph.D.
Chief, Genetic Services Branch
Division of Services for Children with Special Health Needs
Maternal and Child Health Bureau
5600 Fishers Lane, Rm 18-A-19
Rockville, MD 20857
301-443-8604-fax
301-443-1080-phone

Submission check list	
	Cover letter by proponent
	Nomination form
	Copy of references listed on this form

Contact information (proponent)

REFERENCES (continued)	
12	
15	

References

Format Similar to Fact Sheets

CONDITION	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
TYPE of DISORDER	Inborn error of metabolism, fatty acid oxidation disorder
ETHNICITY	Predominantly Caucasians of Northern European ancestry, less frequent in Hispanics, rare in African-Americans, very rare in Orientals
SCREENING METHOD(S)	Tandem mass spectrometry (MS/MS)
NBS STATUS in the US	Screened for in 31 of 51 states, 53% of annual births (as August 2004)

Responses:	90	Valid scores:	1,556	96%	PubMed references (August 2004):	801

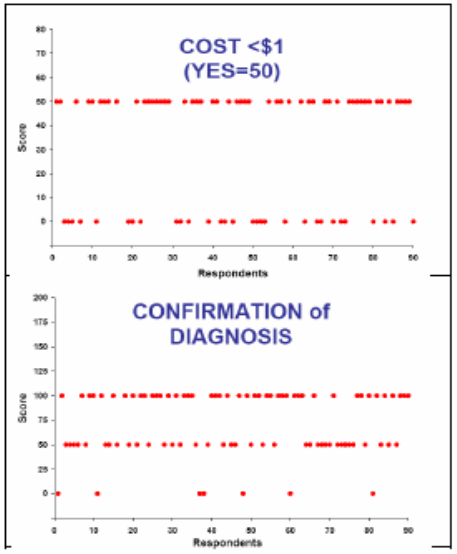
Gene	*ACDM*	Locus	*1p31*	OMIM	*201450*

SURVEY SCORES

Criteria	Consensus	% of max score	LITERATURE AND WEB-BASED EVIDENCE [References]
The condition			
Incidence	>1:25,000	78%	MCAD deficiency occurs in 1:10,000-1:15,000 US newborns, higher if predominant Northern European ancestry [1].
Phenotype at birth	Almost never	91%	Reports of severe neonatal decompensation and sudden unexpected death in exclusively breast-fed newborns [2].
Burden if untreated	Profound	84%	Mortality is 30-50% at first episode [3].
The test			
Screening test	Yes (MS/MS)	100%	MS/MS, precursor ion scan of m/z 85 for acylcarnitine profiling. Primary marker is C8. First reported in 1990 [4].
Doable in DBS or by physical method	Yes	99%	See [4]. 2nd tier DNA analysis of DBS is also available [5].
High throughput	Yes	92%	Up to 500-1,000 specimens per day [6].
Overall cost <$1	Yes (lack of consensus) (*)	63%	Cost likely higher if MS/MS implemented to screen for 1-3 conditions only (CT, MI, NY, RI, VA, WA) [7].
Multiple analytes	Yes	92%	C6, C8, C10:1, C10 acylcarnitines [1,3,4,8,9].
Secondary targets	Yes	74%	GA2 (multiple defects), M/SCHAD, MCKAT [8].
Multiplex platform	Yes	78%	For comprehensive review see [6].
The treatment			
Availability & cost	Widely available	94%	Avoidance of fasting, aggressive treatment of intercurrent illnesses; carnitine supplementation may be useful [3,9,11].
Efficacy of treatment	Potential to prevent ALL negative consequences	80%	Most cases diagnosed by NBS remain asymptomatic with avoidance of fasting [12,13]. Still limited long term data [14].
Benefits of early intervention	CLEAR evidence that early intervention optimizes individual outcome	90%	Expectation of normal growth and development. Significant prevention of mortality [1,3,8,9,11,14,15].
Benefits of early identification	CLEAR benefit to family & society	94%	Identification of affected relatives [16], prevention of costs for care of episodes [1,3,9,13] dismissal of abuse allegations [17].
Prevention of mortality	Yes	99%	Prevention of sudden and unexpected death [2,3,8,11,17].
Confirmation of diagnosis	Limited availability (lack of consensus) (*)	71%	Plasma acylcarnitines and urine acylglycines [18]; genotyping: ~20 labs offer testing for 985A>G; <5 labs provide complete gene sequencing [18-19].
Acute management	Limited availability	80%	Well established emergency protocols [3,9,11].
Simplicity of therapy	Periodic involvement of specialist	77%	No special food or orphan drug required [3,9,11].

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency

CRITERIA OF LEAST CONSENSUS see (*) on first page



INCLUSION CRITERIA

Test available	YES	Type	MS/MS
2ary target of higher scoring condition?			NO
Final score	1799 /2100	% of max score	84%
Rank:	1.00 %ile		
Observed significant discrepancies with literature			NO

ASSESSMENT

Primary target, inclusion in uniform panel

COMMENT

MCAD deficiency had the highest score of the panel of conditions included in the survey. This condition clearly meets the criteria for inclusion in the uniform panel and state programs currently not screening for MCAD deficiency should be strongly encouraged 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.

REFERENCES AND WEB SITES

1. Wang SS et al. Medium chain acyl-CoA dehydrogenase deficiency human genome epidemiology review. Genetics in Medicine. 1999;1:332-9.
2. Rinaldo P et al. Sudden and unexpected neonatal death: A protocol for the postmortem diagnosis of fatty acid oxidation disorders. Sem Perinatol 1999; 23:204-210.
3. Roe CR et al. Mitochondrial fatty acid oxidation disorders. In: Scriver CR et al (eds) The Metabolic and Molecular Bases of Inherited Disease, 8 ed. McGraw-Hill, New York, pp 2297-326, 2001
4. Chace DH et al. Rapid diagnosis of MCAD deficiency: quantitatively analysis of octanoylcarnitine and other acylcarnitines in newborn blood spots by tandem mass spectrometry. Clin Chem 1997; 43:2106-13.
5. McKinney J et al. Rapid screening of the human MCAD gene. Mol Genet Metab 2004; 82:112-120.
6. Chace DH et al. Use of tandem mass spectrometry for multianalyte screening of dried blood specimens from newborns. Clin Chem 2003; 49:1797-1817.
7. National Newborn Screening & Genetics Resource Center: Current newborn conditions by state [updated 07-05-04], http://genes-r-us.uthscsa.edu/
8. Rinaldo P et al. Fatty acid oxidation disorders. Ann Rev Physiol 2002; 64:16.1-26.
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11. Medium chain acyl-CoA dehydrogenase deficiency. In: Nyhan WL, Ozand PT (eds). Atlas of Metabolic Diseases. Chapman & Hall, London, 1998; pp 223-228.
12. Wilcken B et al. Screening for newborn errors of metabolism by tandem mass spectrometry. N Engl J Med 2003; 348:2304-2312.
13. Pandor A et al. Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: A systematic review. Health Technol Assess 2004; 8(12).
14. Dezateux C. Newborn screening for medium chain acyl-CoA dehydrogenase deficiency: evaluating the effects on outcome. Eur J Pediatr 162(Suppl 1):S25-8, 2003.
15. Wilson CJ et al. Outcome of medium chain acyl-CoA dehydrogenase deficiency after diagnosis. Arch Dis Child 1999;80:459-462.
16. Bodman M et al. Medium-chain acyl coenzyme A dehydrogenase deficiency: occurrence in an infant and his father. Arch Neurol 2001;58:811-814.
17. Chace DH et al. Electrospray tandem mass spectrometry for analysis of acylcarnitines in dried postmortem blood specimens collected at autopsy from infants with unexplained cause of death. Clin Chem 2001; 47:1166-1182.
18. GeneTests Laboratory Directory, http://www.geneclinics.org/ ; or UCSD Biochemical genetics Test List, http://biochemgen.ucsd.edu/ucsdw3bg/
19. Andresen BS et al. MCAD mutations identified by MS/MS-based prospective screening of newborns differ from those observed in patients with clinical symptoms: identification and characterization of a new, prevalent mutation that results in mild MCAD deficiency. Am J Hum Genet 2001;68:1408-1416.

MCAD Deficiency

HRSA/ACMG UNIFORM PANEL (DRAFT 01/23/06)
NOMINATION OF CONDITION - Fact Sheet

Name of proponent	Piero Rinaldo	Date	02/13/06
Condition	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency		
Type of disorder	Fatty acid oxidation disorder		
Screening method	Tandem mass spectrometry (MS/MS)		
Treatment strategy	Avoidance of fasting (frequent feedings), low fat diet, carnitine supplementation		

CONDITION	Comment	Gene	*ACDM*	Locus	*1p31*	OMIM	*201450*
Incidence	(Reference required: By pilot screening or clinical identification?) - MCAD deficiency is currently screened in xx% of US newborns (xx/51 states). The incidence is between 1:10,000 and 1:20,000 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. 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 [2]. However, these events occur more frequently in the first 72 hours of life, at a time when results may not yet be available. First onset of symptoms is often after several months or years (see severity below).						
Severity of disease	(Morbidity, disability, mortality) - Up to 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 [X]. Survival may be associated with permanent neurological damage that requires lifetime care and drug treatment.						

TEST	Comment
Screening test(s) to be used	(High volume method, platform) - Tandem mass spectrometry, acylcarnitine (butylated) profiling by parent ion analysis (p85). Informative markers include C6, C8 (primary), C10:1, C10 acylcarnitine species. The following ratios are also useful: C8/C2, C8/C10. A typical MCAD profile shows elevation of all these species with a characteristic pattern (C6<C8>C10; C10:1>C10, C8/C10 ratio >5) but different patterns could be detected. Carriers are detectable biochemically (C6<C8<C10 pattern)
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 elevated C8 at the first screening (N=71,677). Ten of them were reported as abnormal, four were confirmed to be affected, three of the other six were heterozygotes. The performance metrics were as follows: sensitivity: 100%; specificity 99.99%; detection rate: 1:17,994; positive predictive value: 40%; false positive rate: 0.008%
Confirmatory testing	(Reliability, availability) - Confirmatory testing is relatively available and is based on plasma acylcarnitine analysis and urine acylglycine analysis. These tests are highly reliable when properly interpreted. The diagnostic markers are the same acylcarnitine species detected by newborn screening (C6, C8, C10:1, C10, and ratios) and hexanoylglycine/suberylglycine, respectively. Plasma carnitine (total, free) 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. Adequate post-analytical interpretive skills should prevent any significant impact of false positive results. As mentioned above, carriers are likely to be detected by should be properly identified by pattern recognition. Collection of blood spots is a routine form of blood drawing and implies minimal risk.

Nomination of condition (page 2)

TREATMENT	Comment
Modality	(Drug(s), diet, replacement therapy, transplant, other) - 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.
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 habits and is widely available, and inexpensive.
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. Detection of an affected case could conceivably lead to disclosure of non-paternity.

KEY REFERENCES (Specific citations - limit to 15)

1.
2.
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Submit nomination to:

Michele A. Lloyd-Puryear, M.D., Ph.D.
Chief, Genetic Services Branch
Division of Services for Children with Special Health Needs
Maternal and Child Health Bureau
5600 Fishers Lane, Rm 18-A-19
Rockville, MD 20857
301-443-8604-fax
301-443-1080-phone

Submission check list

- [ ] Cover letter by proponent
- [ ] Nomination form
- [ ] Copy of references listed on this form

Contact information (proponent)

Piero Rinaldo, MD, PhD
Biochemical Genetics Laboratory - Hilton 360C
Dept Laboratory Medicine & Pathology - Mayo Clinic
200 First Street SW Rochester MN 55905
(507) 284-6859; Fax (507) 266-2888; rinaldo@mayo.edu

REFERENCES (continued)

12.
13.
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Nomination Form

- Condition
- Test
- Treatment

Condition

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.

Condition

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.

Condition

Severity of Disease

(Morbidity, disability, mortality)

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

Test (High volume method, platform)

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

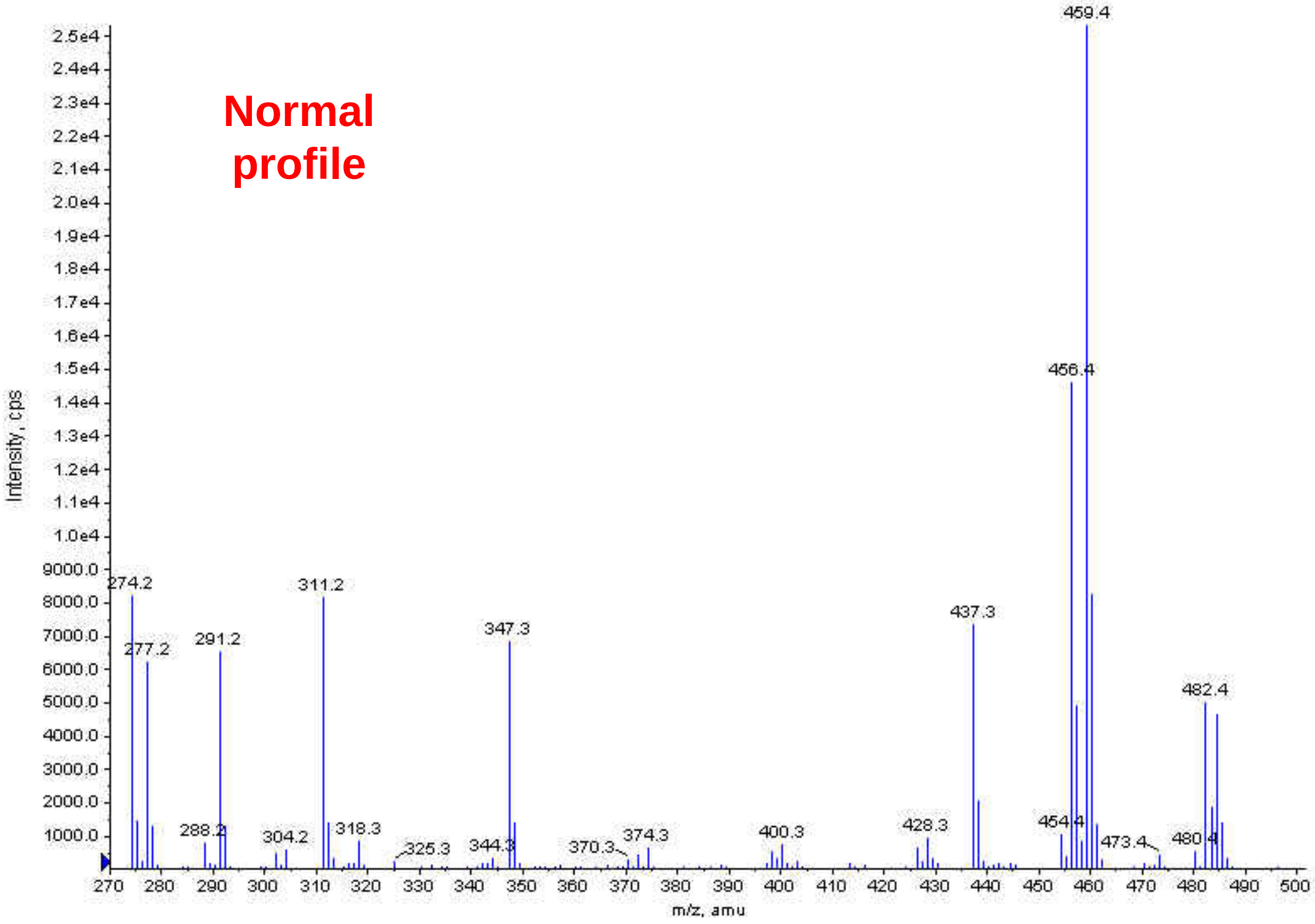
Precursor ion scan of m/z 85 for acylcarnitine profiling.

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
Intensity, cps
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459.4
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274.2
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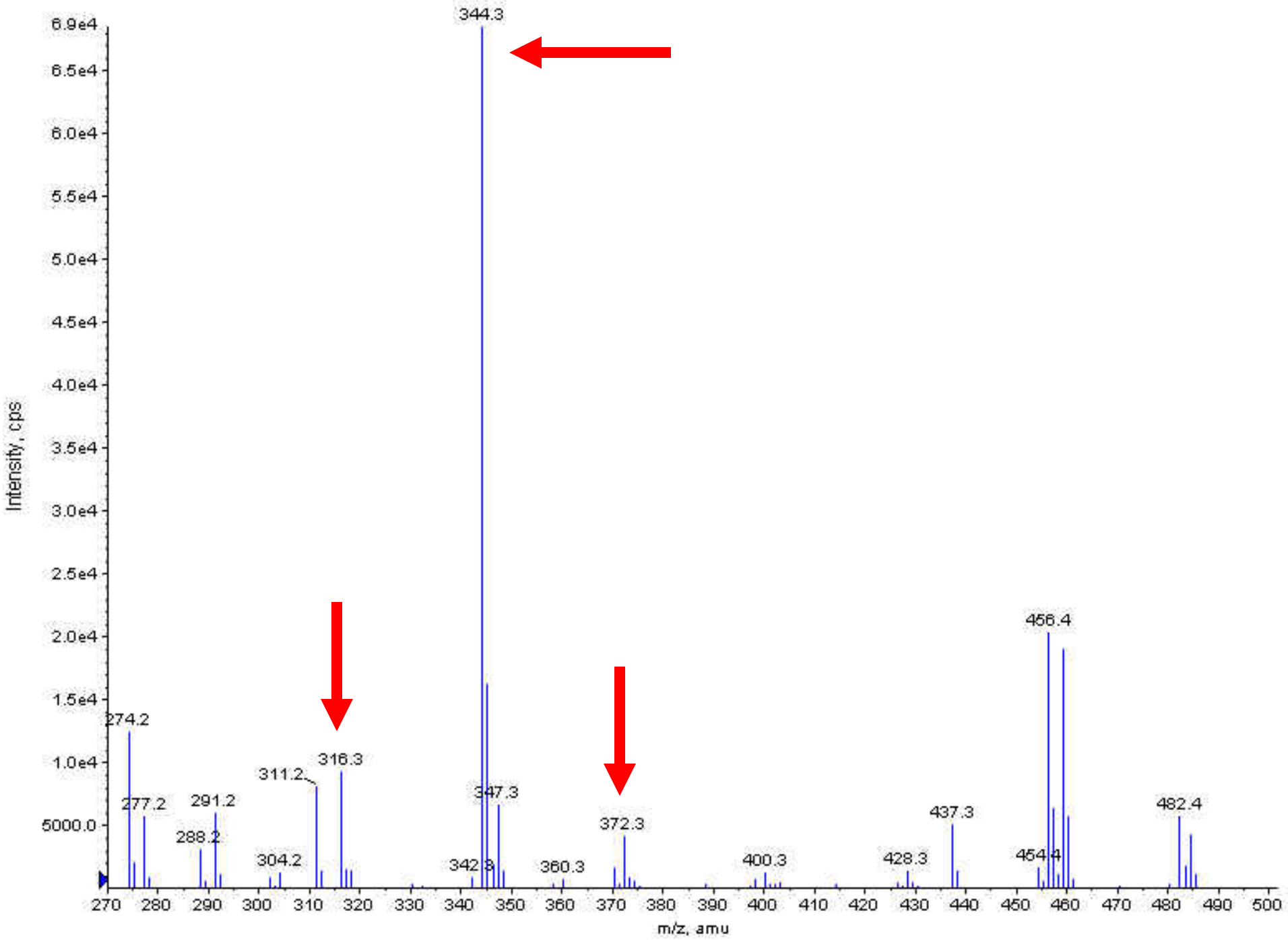
Intensity, cps
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m/z, amu

Test

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.

Test

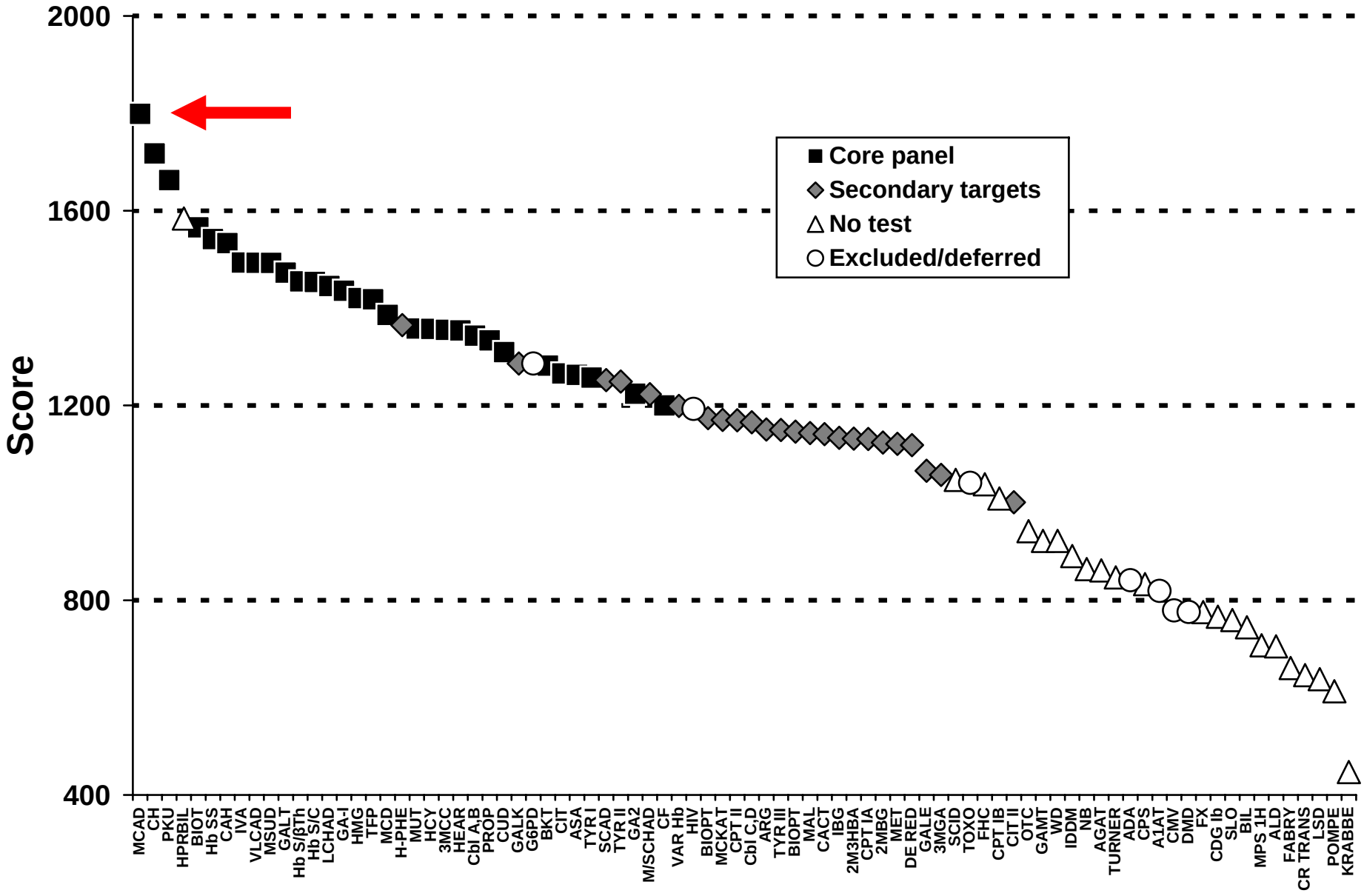
Clinical Validation

(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.

HRSA/ACMG Survey



Laboratory Performance Metrics

(Sensitivity, specificity, detection rate, positive predictive value, false positive rate)

Test

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%

Test

Confirmatory Testing

(Reliability, availability)

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 suberylglycine in urine.

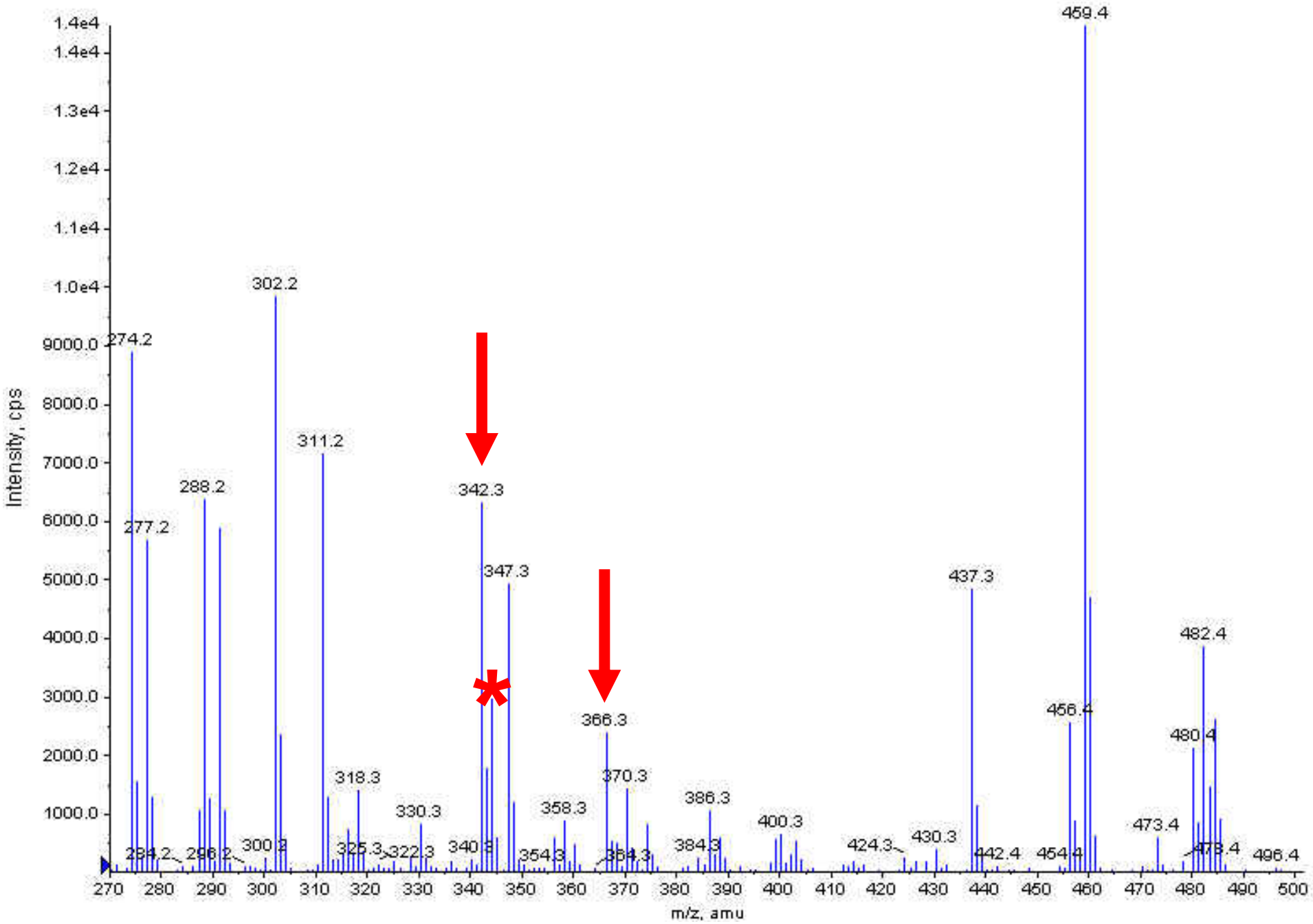
Plasma carnitine and urine organic acids are NOT reliable in asymptomatic patients. Sequencing of the entire gene is required in patients with only one, or none, 985A>G allele.

Test

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.


Intensity, cps
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354.3
384.3

Test

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

Treatment

Modality

(Drug(s), diet, replacement therapy, transplant, other)

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.

Treatment

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

Treatment

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.

Treatment

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.

Treatment

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.

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

NOMINATION OF CONDITION - Fact Sheet

Name of proponent		Date	
Condition			
Type of disorder			
Screening method			
Treatment strategy			

CONDITION	Comment	Gene		Locus		OMIM	
Incidence	(Reference required; By pilot screening or clinical identification?)						
Timing of clinical onset	(Relevance of the timing of newborn screening to onset of clinical manifestations)						
Severity of disease							
TEST							
Screening test(s) to be used							
Modality of screening							
Clinical validation	(Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation)						
Laboratory performance metrics	(Sensitivity, specificity, detection rate, positive predictive value, false positive rate)						
Confirmatory testing	(Reliability, availability)						
Risks	(False positives, carrier detection, invasiveness of method, other)						

Nomination of condition (page 2)

TREATMENT	Comment
Modality	(Drug(s), diet, replacement therapy, transplant, other)
Urgency	(How soon after birth treatment needs to be initiated to be effective)
Efficacy	(Extent of prevention of mortality, morbidity, disability)
	(Any limits of availability)

Ladies and gentlemen,

please start your engines...

to:

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nch
cial Health Needs
ureau
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list

	Cover letter by proponent
	Nomination form
	Copy of references listed on this form

Contact information (proponent)

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REFERENCES (continued)

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