SUPPLEMENT ARTICLE

Naming and Counting Disorders (Conditions) Included in Newborn Screening Panels

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ABSTRACT

The rapid introduction of new technologies for newborn screening is affecting decisions about the disorders (conditions) that are required or offered as an option through public and private newborn screening. An American College of Medical Genetics report to the Health Resources and Services Administration summarized an extensive effort by a group of experts, with diverse expertise within the newborn screening system, to determine a process for selecting a uniform panel of newborn screening disorders. The expert panel did not propose a mechanism for counting or naming conditions. Differences in the nomenclature used to identify disorders have resulted in difficulties in developing a consensus listing and counting scheme for the disorders in the recommended uniform panel. We suggest a system of nomenclature that correlates the screening panel of disorders recommended in the American College of Medical Genetics report with the screening analyte and accepted standardized nomenclature. This nomenclature system is proposed to remove ambiguity and to increase national uniformity in naming and counting screening disorders.

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Key Words
newborn screening, disorders, nomenclature

Abbreviations
ACMG—American College of Medical Genetics
MS/MS—tandem mass spectrometry

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THE RAPID INTRODUCTION of new technologies for newborn screening is affecting decisions about the disorders (conditions) that are required or offered as an option through public and private newborn screening. There is general agreement that it is preferable to have a uniform panel of disorders required and offered nationwide, rather than the variability among programs that exists currently. To provide direction for national uniformity, the American College of Medical Genetics (ACMG)[1] recently recommended a decision-making process and a resultant core panel of disorders to be considered for adoption and implementation by all US newborn screening programs.

Differences in the nomenclature used to identify disorders, sometimes confounded by multiple clinical variations, have resulted in difficulties in developing a consensus listing and counting scheme for the disorders in the recommended uniform panel. For example, confusion results from choosing either the name of the disorder, the name of the analyte deficiency, or the name of the screening analytes in a nonsystematic way. Counting disorders creates even more confusion, because multiple variations of a disorder sometimes are counted in different ways or are not counted at all. The naming and counting problem is especially apparent with multianalyte test systems, such as tandem mass spectrometry (MS/MS) tests for biochemical disorders, that detect simultaneously large numbers of different analytes (and therefore disorders) in a single assay from a single dried blood spot punch.[2,3]

We suggest a system of nomenclature that correlates the screening panel of disorders recommended in the ACMG report with the screening analytes and accepted standardized nomenclature. This classification system would require general use in the newborn screening and subspecialty communities to become a consensus product. Standardization of screening panels, including nomenclature, screening methods, and case definitions, would improve the quality of reported data. Good data quality is necessary for learning more about the natural history of the disorders, validating the utility of the screening strategy, encouraging screening uniformity, and providing for more-uniform program quality assurance. We also identify and comment on concerns related to the fact that some disorders listed in the ACMG report have not yet been identified through newborn screening, although the analytical procedure has been used to detect the disorder among older patients in diagnostic laboratory settings.

METHODS

Background

Newborn screening laboratory testing procedures do not identify disorders specifically; rather, they identify biochemical markers (analytes) that are related to the disorders in question. In some cases, a second analytical process performed with the same sample detects a different analyte, from which more information can be obtained to improve the overall identification process. In most cases, newborn screening involves a single analysis that detects a single marker; in recent years, however, newer technologies have allowed for the simultaneous detection of multiple analytes through a single analytical process. In newborn screening, multianalyte analyses have included flow chemical assays for some metabolic conditions, electrophoretic and chromatographic assays for hemoglobinopathies, and, more recently, MS/MS assays for metabolic conditions. Because of the ability of MS/MS to detect markers that may identify >1 disorder, naming and counting the disorders associated with MS/MS technology have been particularly challenging.

The primary analytes detected through MS/MS newborn screening and the associated disorders are listed in Tables 1 and 2, which illustrate the potential breadth of the naming and counting difficulties. Perhaps the simplest description of the spectrum of disorders detectable through MS/MS newborn screening, which identifies multiple amino acid and acylcarnitine analytes, is the phrase "MS/MS-detectable disorders of amino acid, organic acid, and fatty acid metabolism." However, many, including some physicians, legislators, and parents, seem to prefer a specific list of newborn screening disorders. As a consequence, there has been a competition among screening programs (public and private) to offer the largest number of screening disorders. To some extent, this has been driven by the consumer perception that more is better. Therefore, whereas some newborn screening programs report screening panels that detect 25 to 35 disorders,[4,5] others report detecting >50 disorders[6] by using similar systems and screening for the same analytes. Also, misleading information about the number of disorders covered by a test panel occurs when the number of disorders is inflated by counting disorder variants, while still failing to test for all disorders in the ACMG recommended panel.[7] The difference arises from a lack of uniformity in naming and counting disorders.

ACMG Report

The ACMG report[1] summarized an extensive effort by a group of experts with diverse expertise within the newborn screening system to determine a process for selecting a uniform panel of newborn screening disorders. This expert group recognized that quantification and categorization of newborn screening disorders are imperfect and inconsistent and, until they are standardized, there will continue to be confusion about the extent of screening in individual programs and throughout the nation. The group recommended a common nomenclature for the objective and scientifically valid screening test panel described.

The ACMG expert group reviewed and modified traditional selection criteria for screening disorders,[8] which originated in the 1960s and were established on the basis

TABLE 1 **Nomenclature for Conditions Included in the ACMG Recommended Uniform Panel for Newborn Screening Programs**

Condition/Disorder	ACMG Code	Primary Analyte/Biomarker	Preferred Screening Strategy
Endocrine disorders			
Thyroid disorders			
Primary congenital hypothyroidism	CH	T_4 and TSH	T_4 and TSH immunoassay
Disorders of adrenal steroidogenesis			
Congenital adrenal hyperplasia (MIM 201910) (steroid 21-hydroxylase deficiency [EC 1.14.99.10]), salt-wasting, simple virilizing, or nonclassic	CAH	17-OHP	17-OHP immunoassay
Metabolic disorders			
Organic acid disorders			Acylcarnitines by MS/MS
Propionic acidemia (MIM 606054) (propionyl-CoA carboxylase deficiency [EC 6.4.1.3])	PROP[a]	C3	
Methylmalonic acidemia (MIM 251000) (methylmalonyl-CoA mutase deficiency [EC 5.4.99.2])	MUT[a]	C3	
Methylmalonic acidemia (Cbl A, MIM 251100; Cbl B, MIM 251110; EC 5.4.99.2)	Cbl A,B[a]	C3	
Methylmalonic acidemia (Cbl C, MIM 277400; Cbl D, MIM 277410; EC 5.4.99.2)	Cbl C,D[a]	C3	
Malonic acidemia (MIM 248360) (malonyl-CoA decarboxylase deficiency [EC 4.1.1.9])	MAL	C3DC	
Isobutyrylglycinuria (MIM 604773) (isobutyryl-CoA dehydrogenase deficiency [EC 1.1.1.157])	IBG[a]	C4	
Isovaleric acidemia (MIM 243500) (isovaleryl-CoA dehydrogenase deficiency [EC 1.3.99.10])	IVA[a]	C5	
2-Methylbutyrylglycinuria (MIM 600301) (2-methylbutyryl-CoA dehydrogenase deficiency [EC 1.3.99.12])	2MBG[a]	C5	
3-Methylcrotonyl-CoA carboxylase deficiency I (MIM 210200, MIM 210210, EC 6.4.1.4)	3MCC[a]	C5-OH	
3-Methylglutaconic aciduria (MIM 250950) (3-methylglutaconyl-CoA hydratase deficiency [EC 4.2.18])	3MGA[a]	C5-OH	
3-Hydroxy-3-methyglutaric aciduria (MIM 300438) (3-hydroxy-3-methylglutaryl-CoA lyase deficiency [EC 4.1.3.4])	HMG[a]	C5-OH	
Holocarboxylase synthetase deficiency (MIM 253270) (multiple carboxylase deficiency [EC 6.3.4.11])	MCD[a]	C5-OH and/or C3	
2-Methyl-3-hydroxybutyric aciduria (MIM 300438) (2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency [EC 1.1.1.178])	2M3HBA[a]	C5-OH	
β-Ketothiolase deficiency (MIM 203750) (mitochondrial acetoacetyl-CoA thiolase deficiency [EC 2.3.1.16, EC 2.3.1.9])	βKT	C5:1 and/or C5-OH	
Glutaric acidemia type I (MIM 231670) (glutaryl-CoA dehydrogenase deficiency [EC 1.3.99.7])	GA1	C5DC	
Fatty acid oxidation disorders			Acylcarnitines by MS/MS
Carnitine uptake defect/carnitine transport defect (MIM 212140; Swiss-Prot entries: O76082 and Q9H015)	CUD	CO (free carnitine)	
Short-chain acyl-CoA dehydrogenase deficiency (MIM 201470, EC 1.3.99.2)	SCAD[a]	C4	
Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (MIM 601609, EC 1.1.1.35)	M/SCHAD[b]	C4-OH	
Glutaric acidemia type II (MIM 231680) (multiple acyl-CoA dehydrogenase deficiency [EC 1.5.5.1])	GA2[a]	C4–C18 saturated and unsaturated species	
Medium-chain ketoacyl-CoA thiolase deficiency (MIM 602199, EC 2.3.1.16)	MCAT[b]	C8, C8-OH, and C10-OH	
Medium-chain acyl-CoA dehydrogenase deficiency (MIM 607008, EC 1.3.99.3)	MCAD[a]	C8	
2,4-Dienoyl-CoA reductase deficiency (MIM 222745, EC 1.3.1.34)	DE RED[b]	C10:2	
Very long-chain acyl-CoA dehydrogenase deficiency (MIM 201475, EC 1.3.99.13)	VLCAD	C14:1	
Carnitine palmitoyltransferase I deficiency (MIM 255120, EC 2.3.1.21)	CPT IA[a]	C16 (low)	
Carnitine palmitoyltransferase II deficiency (MIM 255110, EC 2.3.1.21)	CPT II[a]	C16 (high)	
Carnitine acylcarnitine translocase deficiency (MIM 212138; Swiss-Prot entry: O43772)	CACT[a]	C16 (high)	
Long-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (MIM 609016, EC 1.1.1.211)	LCHAD[a]	C16-OH and/or C18:1-OH	
Trifunctional protein deficiency (MIM 609015, EC 1.1.1.211)	TFP[a]	C16-OH and/or C18:1-OH	
Amino acid disorders			Amino acids by MS/MS
Argininemia (MIM 207800) (arginase deficiency [EC 3.5.3.1])	ARG	Arginine	
Argininosuccinic aciduria (MIM 207900) (argininosuccinate lyase deficiency [EC 4.3.2.1])	ASA[a]	Citrulline	

TABLE 1 **Continued**

Condition/Disorder	ACMG Code	Primary Analyte/Biomarker	Preferred Screening Strategy
Citrullinemia, type I (MIM 215700) (argininosuccinate synthase deficiency [EC 6.3.4.5])	CIT[a]	Citrulline	
Citrullinemia, type II (MIM 605814) (citrin deficiency)	CIT II[a]	Citrulline	
Maple syrup urine disease (MIM 248600) (branch-chain ketoacid dehydrogenase complex deficiency [EC 1.2.4.4])	MSUD	Leucine plus isoleucine and/or valine	
Homocystinuria (MIM 236200) (cystathionine β-synthase deficiency [EC 4.2.1.22])	HCY[a]	Methionine	
Hypermethioninemia (MIM 250850) (methionine adenosyltransferase deficiency [EC 2.5.1.6])	MET[a]	Methionine	
Classic phenylketonuria (MIM 261600) (phenylalanine hydroxylase deficiency [EC 1.14.16.1])	PKU[a]	Phenylalanine	
Benign hyperphenylalaninemia (MIM 261600) (phenylalanine hydroxylase deficiency [EC 1.14.16.1])	H-PHE[a]	Phenylalanine	
Biopterin defect in cofactor biosynthesis (MIM 261640) (pyruvoyltetrahydropterin synthase deficiency [EC 4.2.3.12])	BIOPT(BS)[a]	Phenylalanine	
Biopterin defect in cofactor regeneration (MIM 261630) (dihydropteridine reductase deficiency [EC 1.5.1.34])	BIOPT(REG)[a]	Phenylalanine	
Tyrosinemia, type I (MIM 276700) (fumarylacetoacetase deficiency [EC 3.7.1.2])	TYR I[a]	Tyrosine	
Tyrosinemia, type II (MIM 276600) (tyrosine transaminase deficiency [EC 2.6.1.5])	TYR II[a]	Tyrosine	
Tyrosinemia, type III (MIM 276710) (4-hydroxyphenylpyruvate hydroxylase deficiency [EC 1.13.11.27])	TYR III[a]	Tyrosine	
Vitamin disorders			
Biotinidase deficiency (MIM 253260, EC 3.5.1.12)	BIOT	Enzyme/biotin-*p*-aminobenzoic acid	Spectrophotometric (*p*-aminobenzoate)
Hemoglobin disorders			Isoelectric focusing or high performance liquid chromatography or electrophoresis (cellulose acetate and citrate agar)
S,S disease (MIM 603903, MIM 141900)	Hb SS	Hemoglobins	
S,β^0-thalassemia (MIM 141900)	Hb S/βTh	Hemoglobins	
S,C disease (MIM 141900)	Hb S/C	Hemoglobins	
Various other hemoglobinopathies (MIM 141900)	Var Hb	Hemoglobins	
Other disorders			
Galactose disorders			G1P uridyltransferase, G1P, and total galactose
Classic galactosemia (MIM 230400) (galactose-1-phosphate uridyltransferase deficiency [EC 2.7.7.12])	GALT	Enzyme/NADPH	
Galactoepimerase deficiency (MIM 230350) (uridine diphosphate galactose 4-epimerase deficiency [EC 5.1.3.2])	GALE[a]	Galactose	
Galactokinase deficiency (MIM 230200, EC 2.7.1.6)	GALK[a]	Galactose	
Pulmonary disorders			
Cystic fibrosis (MIM 219700) (CF transmembrane conductance regulator defect [MIM 602421])	CF	Immunoreactive trypsinogen and DNA	Immunoassay and polymerase chain reaction; ΔF508, panel of common mutations
Congenital hearing loss			
Hearing loss	HEAR		Otoacoustic emissions and auditory brainstem response

MIM indicates Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db; contains link to Swiss-Prot entries); EC, Enzyme Commission (enzyme nomenclature; www.chem.qmul.ac.uk/iubmb/enzyme/); T_4, thyroxine; TSH, thyroid-stimulating hormone; OHP, hydroxyprogesterone; G1P, galactose-1-phosphate; C3, propionylcarnitine; C3DC, malonylcarnitine; C4, butyryl/isobutyrylcarnitine; C5, isovaleryl/2-methylbutyrylcarnitine; C5-OH, 3-hydroxyisovaleryl/2-methyl-3-hydroxybutyrylcarnitine; C5:1, tiglylcarnitine; C5DC, glutarylcarnitine; C4-OH, 3-hydroxybutyrylcarnitine; C18, stearoylcarnitine; C8, octanoylcarnitine; C8-OH, hydroxyoctanoylcarnitine; C10-OH, hydroxydecanoylcarnitine; C10:1, decenoylcarnitine; C10:2, decadienoylcarnitine; C14:1, tetradecenoylcarnitine; C16, palmitoylcarnitine; C16-OH, 3-hydroxyhexadecanoylcarnitine; C18:1-OH, 3-hydroxyoctadecenoylcarnitine; NADPH, nicotinaminde adenine dinucleotide phosphate (reduced form).

[a] Condition/disorder is identified through the use of secondary biomarkers, biomarker ratios, and/or second-tier testing after the initial screen yields a value outside normal limits for the primary analyte/biomarker.

[b] No documented evidence for detection through a newborn screening program.

TABLE 2 **Nomenclature for Conditions Not Included in the ACMG Recommended Uniform Panel but Screened for by Some Newborn Screening Laboratories**

Condition/Disorder	ACMG Code	Primary Analyte/Biomarker	Preferred Screening Strategy
Endocrine disorders			T_4 and TSH immunoassay
Secondary congenital hypothyroidism	2ºCH	T_4 and TSH	
Thyroid-binding globulin deficiency (MIM 314200)	TBG	T_4 and TSH	
Metabolic disorders			MS/MS
Guanidinoacetate methyltransferase deficiency (MIM 601240, EC 2.1.1.2)	GAMT	Guanidinoacetate	
5-Oxoprolinuria (MIM 266130) (pyroglutamic aciduria) (glutathione synthetase [EC 6.3.2.3])	5OXOPRO	5-Oxoproline	
Ethylmalonic encephalopathy (MIM 602473, EC 1.5.5.1)	EE	Butyrylcarnitine and isovalerylcarnitine	
Nonketotic hyperglycinemia (MIM 605899)	NKH	Glycine	
Hyperornithinemia-hyperammonemia-homocitrullinuria (MIM 238970) (ornithine transporter defect; Swiss-Prot entry: Q9Y619)	HHH[a]	Ornithine and homocitrulline	
Ornithine transcarbamylase deficiency (MIM 311250, EC 2.1.3.3)	OTC[b]	Citrulline (low)	
Carbamoyl phosphate synthetase deficiency (MIM 608307, EC 6.3.4.16)	CPS I[b]	Citrulline (low)	
Hyperprolinemia I (MIM 237000) (proline oxidase deficiency [EC 1.1.1.104])	HP-I[a,b]	Proline	
Hyperprolinemia II (MIM 239510) (pyrroline-5-carboxylate dehydrogenase deficiency [EC 1.5.1.12])	HP-II[a,b]	Proline	
Hemoglobin disorders		Hemoglobins S, DLos Angeles (DPunjab), OArab, A, F, C, D, E, and H	Isoelectric focusing or high performance liquid chromatography or electrophoresis (cellulose acetate and citrate agar)
S,OArab disease (MIM 141900)			
S,D disease (DLos Angeles, DPunjab) (MIM 142000)			
S,β-thalassemia			
S,E disease (MIM 142100)			
F-only (β^0-thalassemia)			
E,β-thalassemia			
C,β-thalassemia			
D,β-thalassemia			
Hemoglobin H disease (α*Thal3* gene deletion) (MIM 141800)			
Hemoglobin E (heterozygous or homozygous) plus α-thalassemia (hemoglobin H disease)			
Various other hemoglobinopathies			
Glucose-6-phosphate dehydrogenase deficiency (MIM 305900, EC 1.1.1.49)	G6PD	Enzyme/NADPH	Fluorescence spectrophotometric
Other disorders			
Congenital toxoplasmosis	TOXO	IgG and IgM antibodies	Immunoassay
HIV	HIV	IgG antibodies	

MIM indicates Online Mendelian Inheritance in Man (www.ncbi.nlm.nih.gov/entrez/query.fcgi?db; contains link to Swiss-Prot entries); EC, Enzyme Commission (enzyme nomenclature; www.chem.qmul.ac.uk/iubmb/enzyme/); T_4, thyroxine; TSH, thyroid-stimulating hormone; NADPH, nicotinaminde adenine dinucleotide phosphate (reduced form).

[a] No documented evidence for detection through a newborn screening program.

[b] Condition/disorder is identified through the use of secondary biomarkers, biomarker ratios, and/or second-tier testing after the initial screen yields a value outside normal limits for the primary analyte/biomarker.

of one-to-one correspondence between screening tests and disorders. A major new criterion in the ACMG screening panel decision matrix is the important recognition that screening benefits the family and society, in addition to the newborn. The ACMG expert group also recognized the impact of multianalyte platforms such as MS/MS in improving the efficiency of newborn screening laboratory testing and therefore the overall newborn screening process. The group used a specially prepared grading sheet and a numeric composite scoring system to evaluate scientific information from various sources, including published literature and expert opinion.[1]

In a multianalyte procedure, it is sometimes possible for >1 disorder to cause similar out-of-range results for a particular analyte. In such cases, screening can only suggest that the patient is at increased risk for one of several possible disorders. Additional diagnostic evaluation and confirmatory testing are required to identify the disorder that caused the suspect results. In the ACMG report, disorders that were above a certain scoring breakpoint were identified as "core" disorders that should be included in every screening program, with scores based on national information and opinion. Because disorders with lower scores can be detected in the differential diagnosis of some of the core disorders, these disorders were identified as "secondary target" disorders and were included in the disorder listing recommended for newborn screening panels. As expected, there was considerable variance in the opinions of the experts, and in their individual scoring, because of the extreme rarity of some of the disorders assessed. However, the differences in the scores for core and secondary target disorders were of minimal statistical difference. Some disorders with significantly lower scores, usually resulting from the lack of a validated screening test, were identified as not currently meeting the requirements for core or secondary target status. Undoubtedly some of these disorders will move to the core or secondary target list once treatments and/or screening tests appropriate for public health usage are available.

Study Methods

To present standardized nomenclature, the ACMG recommended panels of disorders were combined in Table 1 to include core and secondary targets. Table 2 presents disorders that were not selected in the ACMG report for inclusion in the recommended conditions (disorders) lists but are being reported presently by ≥1 US screening program.[9] To eliminate the confusion that results when disorders are identified with different names or according to the defective enzymes (proteins), each disorder has been referenced to the standard nomenclature of the Enzyme Commission[10] and Online Mendelian Inheritance in Man[11] by using their published reference numbers. The preferred testing strategies identified in Table 1 are considered to be appropriate and necessary for the identification and detection of the disorders listed in the combined ACMG core and secondary target list. Primary analytes for disorders are defined as the analytes that must be present outside the reference range for a disorder to be suspected. Secondary analytes are defined as analytes that, if present outside the reference range in addition to an out-of-range primary analyte, increase the risk that a specific disorder is present. A secondary analyte alone may not indicate a specific risk for the disorder in question. For simplicity, ratios of analytes are considered secondary biomarkers and are not listed in Tables 1 and 2, although many are of value in assessment of the significance of elevations in primary analyte levels. Because there is not consensus regarding the way to use secondary analytes (biomarkers) in newborn screening, we chose not to include them in Tables 1 and 2. The preferred screening strategy indicates the preferred method for detecting primary analytes. Because newborn screening tests identify out-of-range levels of primary analytes and not specific disorders, all disorders related to primary analytes are recommended equally, with a footnote stating that secondary biomarkers, biomarker ratios, and other confirmatory tests are required to identify the specific disorder.

RESULTS

For the disorders listed in Tables 1 and 2, the ACMG code for the disorder, the primary analyte, and the preferred screening strategy are shown. Table 2 is included for reference, is identical in format, and provides information similar to that in Table 1, except that these disorders are included in some state newborn screening panels but not in the ACMG recommended panel. In most cases in Tables 1 and 2, the condition/disorder column lists the name of the disorder and the defective enzyme, linked to an established reference number.

Information about the enzymes (proteins) and disorders can be traced easily with the designated reference numbers. Use of this nomenclature system results in easy disorder identification and provides uniformity in describing screening disorders. Furthermore, it allows for identification of any real differences between the panels of disorders identified in listings from different newborn screening programs, with traceable references.

DISCUSSION

The ACMG recommended screening panels were intended not to be final static lists of disorders but to form the basis for a dynamic process of newborn screening program expansion. The selection system developed in the ACMG project allows disorders to be removed or added in a consistent defined way. We suggest that, when disorders are added to screening panels, the traceable nomenclature system presented in Tables 1 and 2 should be used to provide clear identification and naming for the disorder and defective entity. As the natural histories of screened disorders become better defined, information about the value of various primary and secondary analytes for detection of disorders will increase. This will contribute, in turn, to a better understanding of the incidences, clinical presentations, and treatments of the disorders and will provide a better scientific basis for validating the appropriateness of newborn screening.

The appropriateness of including some disorders in the ACMG report, and consequently the list in Table 1, has been questioned by some because the disorders have not yet been identified through newborn screening, although they have been identified among older patients with the same technology. This raises the question of

whether the analyte of interest is sufficiently out of range among newborns to be of use for early detection of the disorder. Specifically, disorders that have not yet been identified through newborn screening include medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency, medium-chain ketoacyl-CoA thiolase deficiency, and 2,4-dienoyl-CoA reductase deficiency. Also considered controversial are some of the amino acid disorders included in Table 2, ie, hyperprolinemia (types I and II) and hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. The ACMG report acknowledged concerns about some of these disorders (Table 1). Because 2,4-dienoyl-CoA reductase deficiency should be revealed by the MS/MS technology used to screen for the core disorders,[1] it was moved from the list of disorders not currently meeting the criteria for newborn screening to the secondary target category. Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency was moved to the secondary target category on the basis of scientific evidence indicating that the natural history of the disorder was not sufficiently understood.[1] Appropriate categorization for these and other rare screening disorders can occur only through more-extensive data accumulation.

In addition, the tyrosinemias, especially tyrosinemia type I, have not been reliably detectable within the first 48 hours of life in most newborn screening programs. This has resulted in a high reported prevalence of transient neonatal tyrosinemia, which is identified as resulting in a significant number of false-positive results from screening programs.[1] The ACMG report acknowledged that there is evidence of poor specificity (very high rates of false-positive results) for tyrosinemia type I.[1] The primary utility for tyrosine measurements, therefore, is as a secondary analyte for determination of the phenylalanine/tyrosine ratio to improve the predictive value for detection of phenylketonuria. Tyrosine values may also be useful for identification of possible liver disease. Screening programs that have mandated a routine second screen at 1 to 2 weeks after birthing center discharge have the opportunity to determine whether a second screen performed later is more reliable than a screen performed at or near birth for detection of disorders such as tyrosinemia type I, the hyperprolinemias, citrullinemia type 2, and hyperornithinemia-hyperammonemia-homocitrullinuria syndrome. Because the reference ranges and resultant cutoff values for many analytes change significantly during the first weeks of life, it is essential to establish specific reference ranges and cutoff values for the age at which the mandated second specimen is collected. This algorithm change is also essential for screening programs that require only a single screen but follow presumptive positive results with a second screen performed a few days later.

CONCLUSIONS

We propose a simple clear system for naming the disorders included in newborn screening programs that should result in more-consistent counting in situations where counting is considered appropriate. The nomenclature system is simple and user-friendly. We also identify the preferred screening strategy or the preferred method for detecting the primary analyte. Acceptance and use of this nomenclature system and screening strategy by newborn screening programs should remove ambiguity and increase national uniformity in naming and counting screening disorders. It should improve the reliability and comparability of any data collected and should lead to an increased understanding of the disorders included in screening programs. We acknowledge that consensus will be necessary before there is general acceptance and use by US newborn screening programs and their associated diagnostic laboratories, and we encourage rapid open discussion of these recommendations.

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