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## **SIMD Position Statement:**

### **Identifying abnormal newborn screens requiring immediate notification of the health care provider**

#### **Background**

Newborn screening is one of the most effective public health programs saving the lives and reducing morbidity of thousands of babies every year.

For effective newborn screening, multiple components of the newborn screening system need to be engaged. Both public health programs and clinical care providers are critical to the outcome of a baby affected with an emergent condition. The newborn screening system includes the pre-analytical components (obtaining and delivering the sample to be analyzed for bloodspot based tests), analytical components (laboratory where the newborn screening testing is performed and results released), post-analytical components (including linkage to clinical care and continuing short and long term follow up), and encompasses all of the system components needed for clinical care.

The overall goal of the newborn screening system is to provide timely identification of babies affected with a screened condition, to enable early treatment and mitigate morbidity and mortality.

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) has recently affirmed the recommendation published in 2006 by the American College of Medical Genetics and Genomics (ACMG) that recommends critical conditions be reported by five days of life. However, there is no definition of critical conditions.

In March 2014 at the annual meeting of the SIMD, SIMD members discussed that having a list of "critical conditions" would facilitate discussion between clinicians and laboratories around the development of protocols for notification of clinicians when a newborn screen is abnormal. The membership therefore requested that the SIMD formulate a statement addressing this issue.

#### **Methods**

A workgroup of SIMD was formed to address the delineation of critical newborn screening conditions. The workgroup consisted of practicing metabolic physicians and a metabolic physician working in a large public

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health NBS program. Metabolic geneticists have unique expertise in the care of patients with inborn errors of metabolism (IEM), offering a perspective that reflects the reality of the clinical care and urgency of treatment that those affected by these conditions would require. A liaison from the Laboratory Standards & Procedures subcommittee of DACHDNC (which was tasked to identify timeliness measures) was included in the workgroup.

This report seeks to identify as “critical” those IEMs that may present acutely in the first weeks of life and require immediate treatment to mitigate morbidity and mortality. It specifically does not address other components of the NBS system. The conditions were identified by review of ACT sheets, and a consensus of the SIMD critical condition workgroup.

The workgroup first undertook a review of the ACT sheets and found the current ACT sheets to have variable information for providers on which conditions are considered critical.

The workgroup met via conference calls on April 23, 2014, May 7, 2014, June 4, 2014, and July 9, 2014. The workgroup defined a “critical condition” as a condition on the recommended uniform newborn screening panel (RUSP) in which acute symptoms or potentially irreversible damage could develop in the first week of life, and for which early recognition and treatment can reduce risk of morbidity and mortality. This definition of critical conditions was utilized for the purpose of determining whether health care provider(s) for a neonate should be informed immediately that a newborn screen is abnormal. A consensus was reached on which conditions required critical notification (including weekends and after hours notification).

In addition, the SIMD workgroup was contacted by the Laboratory Standards & Procedures subcommittee of the DACHDNC and asked to consider identifying the typical time to crisis for newborns with these conditions. The workgroup felt that we were unable to identify these parameters due to concerns identified in the formal position statement.

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**Inborn errors of metabolism listed below, which are on the current recommended uniform screening panel (RUSP), were identified as “critical”, as defined in Methods section above. When a neonate has an abnormal (out of range) screen for one of these conditions it is imperative that immediate referral for appropriate evaluation and management occur.**

Critical disorders can present with an acute crisis in the first week of life, so it is important to have the NBS result as soon as possible, in keeping with current standards of collection for optimal testing (including age of baby and nutritional status). However, these conditions can also present with potentially lethal crisis in the first hours or days of life. It is not possible, even in the most ideal system, to have results of NBS available before clinical presentation of all affected babies, especially since some babies will present even before it is proper to collect the NBS sample. It therefore remains incumbent on the clinician to include IEM in the differential diagnosis of any ill neonate.

### **Critical Core Conditions\* :**

#### **Organic Acid Conditions**

**Propionic Acidemia (PROP)**

**Methylmalonic Acidemia (methylmalonyl-CoA mutase) (MUT)**

**Isovaleric Acidemia (IVA)**

**3-Hydroxy-3-methylglutaric aciduria (HMG)**

**Holocarboxylase synthase deficiency (MCD)**

**β-Ketothiolase deficiency (BKT)**

**Glutaric Aciduria, Type 1 (GA1)**

#### **Fatty Acid Oxidation Disorders**

**Medium Chain Acyl-CoA-dehydrogenase deficiency (MCAD)**

**Very Long chain acyl-CoA dehydrogenase deficiency (VLCAD)**

**Long chain L-3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)**

**Trifunctional protein deficiency (TFP)**

## **Critical Core Conditions\* Continued**

### **Amino Acid Disorders**

**Argininosuccinic Aciduria (ASA)**

**Citrullinemia type 1 (CIT)**

**Maple syrup urine disease (MSUD)**

### **Other**

**Classic Galactosemia (GALT)**

## **Critical Secondary Conditions\***

### **Organic Acid Conditions**

**Methylmalonic acidemia with homocystinuria - Cobalamin C, D (CblC,D)**

### **Fatty Acid Oxidation disorders**

**Carnitine palmitoyltransferase type 1 deficiency (CPT1A)**

**Carnitine palmitoyltransferase type II deficiency (CPT2)**

**Carnitine acylcarnitine translocase deficiency (CACT)**

**Glutaric Aciduria, Type 2 (GA II/MADD)**

### **Amino Acid Disorders**

**Citrullinemia type II (CIT II)**

\*This list relates to the RUSP as of August, 20, 2014, and is restricted to IEM. Any changes in the RUSP might require re-evaluation of this list.

### **Points to consider:**

**A list of critical conditions is an important starting point for discussion between clinicians and laboratories. There remain issues to consider in using this list for development and implementation of specific policies and protocols.**

1) The workgroup approached identifying critical conditions by condition, rather than by analyte, since it is the conditions for which presentation of clinical symptoms is recognized. Utilizing this approach, the workgroup recognized that several non-critical conditions will be identified since the same key analyte is elevated. Some states, but not all, have second-tier testing to distinguish between various conditions that share the same elevated analyte.

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2) The workgroup recognized that there were several conditions that were considered secondary targets of NBS that met the criteria of being in need of critical notification.

3) The workgroup also noted that there is some scaling in response to an out-of-range elevated newborn screen. Clinical response may depend on the level of elevation of an analyte, the pattern of elevated analytes, or the ratio of elevated analytes. Two caveats noted included that some newborn screening laboratories do not report quantitative values, and others utilize second tier testing to distinguish between conditions.

4) The workgroup also recognized that in these clinical conditions there is heterogeneity in the severity of the conditions, with a spectrum of clinical manifestations and analyte values which may or may not be obvious in the newborn period. Each condition on this list is recognized as having a significant risk of catastrophic presentation in the first week of life; however many babies with these "critical" conditions may be asymptomatic in the first weeks of life. In addition, some babies with conditions on the RUSP but not on this list may in some cases present in the first week of life. It is important that organizations using this list for the purposes of making recommendations and policy be aware of this clinical variability.

5) The workgroup also noted that two screen states may have different responses to out-of-range results based on first or second screen results. For example, in Texas, if the babies first screen GALT is normal, a second screen with an out-of-range GALT value would not be considered a critical notification, while an out-of-range GALT value on the first screen would be considered a critical notification.

**SIMD Critical Condition Workgroup Members:**

Debra Freedenberg – Chair

Susan Berry

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James Gibson

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