NewSTEPs

A Program of the Association of Public Health Laboratories™

Case Definitions for Newborn Screening

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Metabolic Conditions

Case Definitions Tables

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Propionic Acidemia (PROP)

Propionic Acidemia

Classification	Urine organic acids	Plasma Acylcarnitines	Mutation analysis
Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)
Definite	Presence of --methylcitrate and - +/-3OH propionic acid, propionyl glycine, -tiglyglycine and Absence of: -MMA and - methylcrotonyl glycine	Elevated C3	Untested or unknown
Probable	Presence of -3-OH propionic and Absence of: -MMA and -methylcrotonyl glycine	Elevated C3	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]
Possible	Presence of -3-OH Propionic and Absence of -MMA and -methylcrotonyl glycine	Elevated C3	Untested or unknown
Possible	Presence of -3-OH propionic and Absence of -MMA and -methylcrotonyl glycine	Elevated C3	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)
Possible	Presence of -3-OH propionic and Absence of -MMA and -methylcrotonyl glycine	Elevated C3	1 known disease causing variant (Allele 1 - variant known to be disease causing)
Possible	Absence of -MMA and -methylcrotonyl glycine	Elevated C3	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)
Possible	Presence of -3-OH propionic and Absence of -MMA and -methylcrotonyl glycine	Elevated C3	No variants found

Methylmalonic Acidemia (MMA)

MMA; (CblA; CblB, mut-; mut0; CblDv2)

Classification	Urine or serum organic acids	Plasma Acylcarnitines	Maternal Studies	Infant chemistries/studies	Mutation analysis	Enzyme analysis
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	complementation studies consistent with corresponding disease
Definite	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and -Normal homocysteine	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and -Normal homocysteine	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Probable	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and -Normal homocysteine	untested or unknown	Untested or unknown
Probable	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and -Normal homocysteine	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown

	Possible	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and -Normal homocysteine	None found	Untested or unknown
	Possible	Elevated MMA for age	Elevated C3	Untested or unknown	-Absence of B12 deficiency and -Normal homocysteine	N/A	Untested or unknown

Methylmalonic Acidemia (MMA) with Homocystinuria (HCY)

MMA with Homocystinuria; (CblC; CblDv1; CblF; CblD)

Classification	Urine or serum organic acids	Plasma Acylcarnitines	Maternal Studies	Infant chemistries/studies	Mutation analysis	Enzyme analysis
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	complementation studies consistent with corresponding disease
Definite	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and - Elevated homocysteine	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and -Elevated homocysteine	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown	Untested or unknown
Probable	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and -Elevated homocysteine	untested or unknown	Untested or unknown
Probable	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and - Elevated homocysteine	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
Possible	Elevated MMA for age	Elevated C3	Absence of B12 deficiency	-Absence of B12 deficiency and - Elevated homocysteine	None found	Untested or unknown
Possible	Elevated MMA for age	Elevated C3	Untested or unknown	Absence of B12 deficiency and - Elevated homocysteine	N/A	Untested or unknown

Holocarboxylase Synthetase Deficiency (MCD)

Holocarboyase Synthetase Deficiency or other biotin disorders

Classification	Urine organic acids	Plasma Acylcarnitines	Infant chemistries/studies	Mutation analysis	Enzyme analysis
Definite	Untested or unknown	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	enzyme activity on fibroblasts or WBCs consistent with disease
Definite	Elevated -3OH Isovaleric and -3OH Propionic and - 3methylcrotonyl glycine	elevated -C3; and -C5-OH	Normal biotinidase studies	Untested or unknown	Untested or unknown
Possible	Elevated -3OH Isovaleric and - 3methylcrotonyl glycine	elevated -C3; and -C5-OH	Normal biotinidase studies	Untested or unknown	Untested or unknown
Possible	Elevated -propionyl glycine and - 3methylcrotonyl glycine	elevated -C3; and -C5-OH	Normal biotinidase studies	Untested or unknown	Untested or unknown
Possible	Normal	elevated -C3; and -C5-OH	Normal biotinidase studies	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
Possible	Normal	elevated -C3; and -C5-OH	Normal biotinidase studies	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown

Isovaleric Acidemia (IVA)

Isovaleric Acidmeia

Classification	Urine organic acids	Plasma Acylcarnitines	Mutation analysis	Enzyme analysis
Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	enzyme activity on fibroblasts or WBCs consistent with disease
Definite	Elevated - isovaleryl glycine and - 3-OH isovaleric	elevated C5	Untested or unknown	Untested or unknown
Definite	Elevated isovaleryl glycin	elevated C5	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Possible	Elevated isovaleryl	elevated C5	Untested or unknown	Untested or unknown
Possible	Elevated isovaleryl	elevated C5	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
Possible	Elevated isovaleryl	elevated C5	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown

Glutaric Cidemia (GA)

Glutaric Acidemia Type I

Classification	Urine or serum organic acids	Plasma Acylcarnitines	Mutation analysis	Enzyme analysis
Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	enzyme activity consistent with disease
Definite	Elevated - 3-OH Glutaric and - Glutaric	elevated C5 -DC	Untested or unknown	Untested or unknown
Probable	Elevated - 3-OH Glutaric	elevated C5 –DC	Untested or unknown	Untested or unknown
Probable	Elevated glutaric	elevated C5 -DC	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Possible	Elevated glutaric	elevated C5 -DC	Untested or unknown	Untested or unknown

Primary Carnitine Deficiency/ Carnitine Uptake Defect (CUD)

Primary Carnitine Deficiency/ Carnitine Uptake Defect

Classification	Urine Car	Plasma Carnitine	Special Circumstance	Mutation analysis	Enzyme analysis
Definite	Untested or unknown	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	enzyme activity consistent with disease
Definite	Elevated fractional	Low free carnitine	Secondary carnitine loss ruled out	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Low free carnitine	Secondary carnitine loss ruled out	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Possible	Untested or unknown	Low free carniti	Secondary carnitine loss ruled out	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
Possible	Untested or unknown	Low free carnitine	Secondary carnitine loss ruled out	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Possible	Untested or unknown	Low free carnitine	Secondary carnitine loss ruled out	None found	Untested or unknown
Possible	Untested or unknown	Low free carnitine	Secondary carnitine loss ruled out	Untested or unknown	Untested or unknown

Very long-chain acyl-CoA Dehydrogenase Deficiency (VLCAD)

VLCAD

Classification	Plasma Acylcarnitines	Mutation analysis	Functional Studies
Definite	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Functional fibroblast or Enzyme analysis consistent with VLCAD
Definite	Elevated -C14:1 (on more than one sample) and -C14:2 and -C14	Untested or unknown	Untested or unknown
Definite	Elevated -C14:1 (on more than one sample)	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Elevated -C14:1 (on more than one sample) and -C14:2	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Probable	Elevated -C14:1 (on more than one sample)	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Probable	Elevated -C14:1 (on more than one sample) and -C14:2	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
Possible	Elevated -C14:1 (on more than one sample) and - C14:2	Untested or unknown	Untested or unknown

Very long-chain acyl-CoA Dehydrogenase Deficiency (VLCAD)

	Classification	Plasma Acylcarnitines	Mutation analysis	Functional Studies
VLCAD	Possible	Elevated -C14:1 (on more than one sample) and -C14:2	No variants found	Untested or unknown
	Possible	Elevated C14:1 on more than one sample	Untested or unknown	Untested or unknown
	Possible	Elevated C14:1 on more than one sample	No variants found	Untested or unknown
	Possible	Elevated C14:1 on more than one sample	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown

Trifunctional Protein Deficiency (TFP)-Inclusive of LCHAD

Trifunctional Protein Deficiency- Inclusive of LCHAD

Classification	Urine Organics	Plasma Acylcarnitines	Mutation analysis	Functional Studies
Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Functional fibroblast or Enzyme analysis consistent with LCHAD or TFP
Definite	Untested or unknown	Elevated: -C16-OH (on more than one specimen) and -C16:1-OH and -C18-OH and -C18:1-OH	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Elevated -C12-OH dicarboxylic and -C10-OH dicarboxylic	Elevated: -C16-OH (on more than one specimen)and -C16:1-OH and -C18-OH and -C18:1-OH	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Elevated: -C16-OH (on more than one specimen) and -C16:1-OH and -C18-OH and -C18:1-OH	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
Probable	Untested or unknown	Elevated: -C16-OH (on more than one specimen) and -C16:1-OH and -C18-OH and -C18:1-OH	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Possible	Untested or unknown	Elevated: -C16-OH (on more than one specimen) and -C16:1-OH and -C18-OH and -C18:1-OH	No variants found	Untested or unknown
Possible	Untested or unknown	Elevated: -C16-OH (on more than one specimen) and -C16:1-OH and -C18-OH and -C18:1-OH	Untested or unknown	Untested or unknown
Possible	Elevated -C12-OH dicarboxylic and -C10-OH dicarboxylic	Untested or unknown	Untested or unknown	Untested or unknown

Trifunctional Protein Deficiency (TFP)-Inclusive of LCHAD

	Classification	Urine Organics	Plasma Acylcarnitines	Mutation analysis	Functional Studies
Trifunctional Protein Deficiency-Inclusive of LCHAD	Possible	Elevated -C12-OH dicarboxylic and -C10-OH dicarboxylic	Untested or unknown	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
	Possible	Untested or unknown	Elevated: -C16-OH (on more than one specimen)	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown

Argininosuccinic Aciduria (ASA)

Argininosuccinic Aciduria (ASA)	Classification	Plasma or urine amino acids	Mutation analysis	Enzyme Studies
	Definite	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
	Definite	Untested or unknown	Untested or unknown	Enzyme analysis consistent with disease
	Definite	Elevated -ASA and -Citrulline	Untested or unknown	Untested or unknown
	Definite	Elevated ASA	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
	Possible	Elevated Citrulline	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
	Possible	Elevated Citrulline	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown

Citrullinemia, type 1-Exclusive of Citrin Deficiency (CIT)

	Classification	Plasma amino acids	Blood Ammonia Levels	Mutation analysis	Enzyme Studies
Citrullinemia Type I- exclusive of Citrin deficiency	Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and	Untested or unknown
	Definite	Untested or unknown	Untested or unknown	Untested or unknown	Enzyme analysis consistent with
	Definite	Elevated Citrulline and Absent ASA	Untested or unknown	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and	Untested or unknown
	Definite	Elevated Citrulline and Absent ASA	Elevated	Untested or unknown	Untested or unknown
	Probable	Elevated Citrulline and Absent ASA	Untested or unknown	1 known disease causing variant (Allele 1 - variant known to be	Untested or unknown
	Probable	Elevated Citrulline and Absent ASA	Untested or unknown	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 –	Untested or unknown
	Possible	Elevated Citrulline and Absent ASA	Untested or unknown	Untested or unknown	Untested or unknown

3-Methylcrotonyl-CoA (3-MCC)

3-MCC

Classification	Urine organic acids	Plasma Acylcarnitines	Maternal Studies	Mutation analysis	Enzyme analysis
Definite	Untested or unknown	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	enzyme activity consistent with disease
Definite	Elevated 3-OH Isovaleric with or without elevated 3-methylcrotonyl glycine	elevated C5 -OH	Maternal deficiency tested and ruled out	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Elevated 3-OH Isovaleric with or without elevated	elevated C5 -OH	Maternal deficiency tested and ruled out	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Probable	Elevated - 3-OH Isovaleric and - 3-methylcroton	elevated C5 -OH	Maternal deficiency tested and ruled out	Untested or unknown	Untested or unknown
Possible	Elevated - 3-OH Isovaleric and - 3-methylcroton	Untested or unknown	Maternal deficiency tested and ruled out	Untested or unknown	Untested or unknown
Possible	Untested or unknown	elevated C5 –OH	Maternal deficiency tested and ruled out	Untested or unknown	Untested or unknown

Tyrosinemia, Type 1 (TYR 1)

	Classification	Urine or Serum studies	Mutation analysis	Enzyme Studies
Tyrosinemia type I	Definite	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
	Definite	Untested or unknown	Untested or unknown	Enzyme analysis consistent with FAH enzyme deficiency
	Definite	Elevated Succinylacetone	Untested or unknown	Untested or unknown
	Possible	Elevated tyrosine and Normal Succinylacetone	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
	Possible	Elevated Tyrosine and Normal Succinylacetone	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
	Possible	Elevated Tyrosine and Normal Succinylacetone	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown

Medium-chain acyl-CoA Dehydrogenase Deficiency (MCAD)

MCAD

Classification	Urine Organics or aclyglycines	Plasma Acylcarnitines	Mutation analysis	Functional Studies
Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or	Untested or unknown	Functional fibroblast or
Definite	Elevated ***hexanoylglycine***	Elevated: -C8 and -C8>C10 and -C8 >C6 and -C6 and -C10	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Elevated: -C8 and -C8>C10 and -C8 >C6 and -C6 and -C10	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Untested or unknown	Elevated C8 on repeat testing	1 known disease causing variant and 1 variants of uncertain significance in the same gene (Allele 1 - variant known to be disease causing and Allele 2 - variant of unknown significance)	Untested or unknown
Probable	Elevated ***hexanoylglycine***	Elevated C8 on repeat testing	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
Probable	Untested or unknown	Elevated C8 on repeat testing	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Possible	Elevated ***hexanoylglycine***	Elevated C8 on repeat testing	No variants found	Untested or unknown
Possible	Elevated ***hexanoylglycine***	Untested or unknown	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Possible	Elevated ***Hexanoylglycine***	Untested or unknown	No variants found	Untested or unknown
Possible	Untested or unknown	Elevated C8 on repeat testing	No variants found	Untested or unknown

	Possible or Carrier	Untested or unknown	Elevated C8	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown
	Possible or Carrier	Elevated ***Hexanoylglycine***	Normal	1 known disease causing variant (Allele 1 - variant known to be disease causing)	Untested or unknown

Maple Syrup Urine Disease (MSUD)

MSUD

Classification	Plasma amino acids	Urine Organic acids	Mutation analysis	Enzyme Studies
Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Enzyme analysis consistent with MSUD
Definite	Elevated Alloisoleucine and Leu, and Val, and Ileu	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Elevated Alloisoleucine	Untested or unknown	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Elevated Alloisoleucine	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Elevated Leu and Ile and Val and Leu>Val	Elevated 2-ketoisocaproic acid and 2-OH Isovaleric and 2-ketomethyl valeric acid	Untested or unknown	Untested or unknown
Possible	Elevated Leu and Ile and Val and Leu>Val	Untested or unknown	Untested or unknown	Untested or unknown

Cystathionine Beta-Synthase (CBS) Deficiency

CBS deficiency

Classification	Plasma amino acids	Mutation analysis	Enzyme Studies
Definite	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Enzyme analysis consistent with CBS
Definite	Elevated -Methionine and -Homocystine	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]	Untested or unknown
Probable	Elevated -Methionine and -Homocystine	2 variants of uncertain significance in the same gene (Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance)	Untested or unknown
Probable	Elevated -Methionine and -Homocystine	1 known disease causing variant and 1 variant of uncertain significance in the same gene (Allele 1 - variant known to be disease causing and Allele 2 - variant of unknown significance)	Untested or unknown
Possible	Elevated -Methionine and -Homocystine	Untested or unknown	Untested or unknown

Benign Hyperphenylalaninemia (H-PHE)

HyperPhe

Classification	Plasma amino acids	Special Studies	Mutation analysis	Enzyme Studies
Definite	Untested or unknown	Untested or unknown	2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Enzyme analysis consistent with PAH
Definite	Elevated Phe (>120umol/L on unrestricted diet) and Phe/Tyr ratio	Normal biopterin studies	Untested or unknown	Untested or unknown
Possible	Elevated Phe (>120umol/L on unrestricted diet) and Phe/Tyr ratio	Untested or unknown	Untested or unknown	Untested or unknown

Biotinidase Deficiency (BIOT)

	Disorder	Classification	Enzyme Levels	Mutation analysis
Biotinidase Deficiency	Profound	Definite	Untested or unknown	2 variants known to be associated with profound enzyme deficiency in the same gene (Allele 1 – variant known to be associated with profound enzyme deficiency and Allele 2 – variant known to be associated with profound enzyme deficiency)
	Partial	Definite	Untested or unknown	1 variant known to be associated with profound enzyme deficiency and 1 Known to be associated with partial enzyme deficiency [‘mild’ mutation]
	Partial	Definite	Untested or unknown	2 variants known to be associated with partial enzyme deficiency [‘mild’ mutation] (Allele 1 and allele – variant known to be associated with partial enzyme deficiency [‘mild’ mutation (D444H)]
	Profound	Probable	<10% normal activity	Untested or unknown
	Partial	Probable	10-30% normal activity	Untested or unknown

Classic Galactosemia (GALT)

Classic Galactosemia

Classification	GALT Levels	Gal-1-P level	Urine Galactitol	Mutation analysis
Definite				2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)
Definite		Elevated		2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]
Definite			Elevated	2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]
Definite		Elevated		2 variants of uncertain significance in the same gene [Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance]
Definite			Elevated	2 variants of uncertain significance in the same gene [Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance]
Definite		Elevated		1 known disease causing mutation and 1 mutation of uncertain significance gene (Allele 1 – variant known to be disease causing and Allele 2 – and Allele 2 – variant of unknown significance)
Definite			Elevated	1 known disease causing mutation and 1 mutation of uncertain significance gene (Allele 1 – variant known to be disease causing and Allele 2 – and Allele 2 – variant of unknown significance)
Probable		Elevated		
Probable			Elevated	
Probable				1 known disease causing mutation (Allele 1 – variant known to be disease causing)
Probable				2 variants of uncertain significance in the same gene - predicted to be pathogenic [Allele 1 - variant of unknown significance (predicted to be pathogenic) and Allele 2 – variant of unknown significance (predicted to be pathogenic)]
Probable	<10%			2 variants of uncertain significance in the same gene [Allele 1 - variant of unknown significance and Allele 2 – variant of unknown significance]
Probable	<10%			

Variant Galactosemia

Biotinidase Deficiency

Classification	GALT Levels	Gal-1-P level	Urine Galactitol	Mutation analysis	Protein Phenotyping
Definite				1 known classic galactosemia disease causing mutation and 1	
Definite	10%-30%	Elevated		1 known disease causing mutation and 1 mutation of uncertain significance-	
Definite	10%-30%		Elevated	1 known disease causing mutation and 1 mutation of uncertain significance-	
Definite	10%-30%	Elevated			phenotype consistent with variant
Definite	10%-30%		Elevated		phenotype consistent with variant
Definite	10%-30%	Elevated		1 known disease causing mutation and 1 mutation of uncertain significance	
Definite	10%-30%		Elevated	1 known disease causing mutation and 1 mutation of	
Probable	10%-30%				phenotype consistent with variant
Possible	10%-30%				

Arginase Deficiency

Arginase Deficiency

Classification	Plasma amino acids	Mutation analysis	Enzyme Studies
Definite		2 known disease causing variants in the same gene (Allele 1 – variant known to be disease causing and Allele 2 – variant known to be disease causing)	
Definite			Enzyme analysis consistent with Arginase deficiency
Probable	Elevated Arginine	1 known disease causing mutation	
Possible	Elevated Arginine		

Endocrinology Disorders

Case Definitions Tables

September 29, 2013

Definitions created by panel of experts between June 2011 and September 2013. This project was funded in part by Cooperative Agreement # U22MC24078 from the Health Resources and Services Administration (HRSA).

Primary Congenital Hypothyrodism (CH)

	Category	Serum TSH mU/L*	Serum Total or Free T4*
Primary Congenital Hypothyroidism	Definite	TSH > 10	< age established reference range
	Probable	TSH > 10	normal T4/total T4
	Probable	TSH > 10	Untested or unknown
	Possible**	TSH 6-10	< age established reference range
	Possible **	TSH 6-10	Normal
	Possible **	TSH 6-10	Untested or unknown
	Incomplete	Untested or unknown	Untested or unknown
	Incomplete	Untested or unknown	< age established reference

Secondary Congenital Hypothyroidism (CH)

	Category	Serum TSH mU/L*	Serum Total or Free T4*	Other studies
Secondary Congenital Hypothyroidism	Definite	TSH < 10	< age established reference	documentation of other pituitary hormone deficiencies or midline defects
	Probable**	TSH < 10	< age established reference range	no other pituitary hormone deficiencies or midline defects
	Possible	Untested or unknown	< age established reference range	Documentation of other pituitary hormone deficiencies or midline defects
	Possible	TSH<10	Untested or unknown	Documentation of other pituitary hormone deficiencies or midline defects
	Incomplete	Untested or unknown	Untested or unknown	Documentation of other pituitary hormone deficiencies or midline defects
	Incomplete	TSH<10	Untested or unknown	no other pituitary hormone deficiencies or midline defects
	Incomplete	Untested or unknown	< age established reference range	no other pituitary hormone deficiencies or midline defects

Thyroxine-binding Globulin (TBG) or other Protein Binding Defect

TBG or other Protein Binding Defect	Category	Serum TSH mU/L	Serum Free T4	Serum Total T4	Other studies
	Definite	normal	Normal for age	Low for age	Low TBG
	Definite	normal	Normal for age	Low for age	increased T3 or T4 resin uptake

* The results referenced should be obtained before the initiation of therapy.

** Since there can be overlap in these 2 categories (possible primary or probable secondary congenital hypothyroidism) based on the laboratory values, the treating clinician should determine which category.

21-Hydroxylase Deficiency – Classical Salt Wasting

21-Hydroxylase Deficiency – Classical Salt Wasting

Category	Serum 17-OHP - baseline or ACTH stimulated*	Urinary steroid profiling	Serum Sodium mEq/L	Plasma Renin Activity	CYP21A2 Mutation Analysis	If available - Supportive Clinical or Laboratory Evidence
Definite	> 10,000	Untested or unknown	< 135	Untested or unknown	Untested or unknown	Evidence of salt wasting (present in shock or severe failure to thrive)
Definite	> 10,000	Untested or unknown	<135	Untested or unknown	Untested or unknown	ambiguous genitalia in 46, XX
Definite	> 10,000	Untested or unknown	<135	Untested or unknown	Untested or unknown	other hormonal evidence of CAH
Definite	> 10,000	Untested or unknown	Untested or unknown	Elevated for age	Untested or unknown	Evidence of salt wasting (present in shock or severe failure to thrive)
Definite	> 10,000	Untested or unknown	Untested or unknown	Elevated for age	Untested or unknown	ambiguous genitalia in 46, XX
Definite	> 10,000	Untested or unknown	Untested or unknown	Elevated for age	Untested or unknown	other hormonal evidence of CAH
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	two classic genemutations or deletions *in trans*	Evidence of salt wasting (present in shock or severe failure to thrive)
Definite	Untested or unknow	Untested or unknown	Untested or unknown	Untested or unknown	two classic gene mutations or deletions *in trans*	ambiguous genitalia in 46, XX
Definite	Untested or unknow	Untested or unknown	Untested or unknown	Untested or unknown	two classic gene mutations or deletions *in trans*	other hormonal evidence of CAH
Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	Untested or unknown	Untested or unknown	Untested or unknown	Evidence of salt wasting (present in shock or severe failure to thrive)
Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	Untested or unknown	Untested or unknown	Untested or unknown	ambiguous genitalia in 46, XX

21-Hydroxylase Deficiency – Classical Salt Wasting

	Category	Serum 17-OHP - baseline or ACTH stimulated*	Urinary steroid profiling	Serum Sodium mEq/L	Plasma Renin Activity	CYP21A2 Mutation Analysis	If available - Supportive Clinical or Laboratory Evidence
21-Hy21-Hydroxylase Deficiency – Classical Salt Wasting	Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	Untested or unknown	Untested or unknown	Untested or unknown	other hormonal evidence of CAH
	Probable	1,000 -10,000	Untested or unknown	< 135	Untested or unknown	Untested or unknown	Evidence of salt wasting (present in shock or severe failure to thrive)
	Probable	1,000 -10,000	Untested or unknown	< 135	Untested or unknown	Untested or unknown	ambiguous genitalia in 46,XX
	Probable	1,000 -10,000	Untested or unknown	< 135	Untested or unknown	Untested or unknown	other hormonal evidence of CAH
	Probable	1,000 -10,000	Untested or unknown	Untested or unknown	Elevated for age	Untested or unknown	Evidence of salt wasting (present in shock or severe failure to thrive)
	Possible	1,000 -10,000	Untested or unknown	Untested or unknown	Elevated for age	Untested or unknown	ambiguous genitalia in 46,XX
	Possible	1,000 -10,000	Untested or unknown	Untested or unknown	Elevated for age	Untested or unknown	other hormonal evidence of CAH

21-Hydroxylase Deficiency-Classical Simple Virilizing

21-Hydroxylase Deficiency – Classical Simple Virilizing	Category	Serum 17-OHP - baseline or ACTH stimulated*	Urinary Steroid profiling	Serum Sodium mEq/L	Plasma Renin Activity	CYP21 A2 Mutation Analysis	If available - Supportive Clinical or Laboratory Evidence
	Definite	>10,000	Untested or unknown	>135	Untested or unknown	Untested or unknown	Ambiguous genitalia in 46,XX
	Definite	>10,000	Untested or unknown	>135	Untested or unknown	Untested or unknown	no evidence of salt wasting
	Definite	>10,000	Untested or unknown	>135	Untested or unknown	Untested or unknown	other hormonal evidence of CAH
	Definite	>10,000	Untested or unknown	Untested or unknown	Normal for age	Untested or unknown	Ambiguous genitalia in 46,XX
	Definite	>10,000	Untested or unknown	Untested or unknown	Normal for age	Untested or unknown	no evidence of salt wasting
	Definite	>10,000	Untested or unknown	Untested or unknown	Normal for age	Untested or unknown	other hormonal evidence of CAH
	Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	>135	Untested or unknown	Untested or unknown	Ambiguous genitalia in 46,XX
	Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	>135	Untested or unknown	Untested or unknown	no evidence of salt wasting
	Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	>135	Untested or unknown	Untested or unknown	other hormonal evidence of CAH
	Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	Untested or unknown	Normal for age	Untested or unknown	Ambiguous genitalia in 46,XX

21-Hydroxylase Deficiency-Classical Simple Virilizing

Category	Serum 17-OHP - baseline or ACTH stimulated*	Urinary Steroid profiling	Serum Sodium mEq/L	Plasma Renin Activity	CYP21A2 Mutation Analysis	If available - Supportive Clinical or Laboratory Evidence
Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	Untested or unknown	Normal for age	Untested or unknown	no evidence of salt wasting
Definite	Untested or unknown	(mass spectrometry) indicative of 21-Hydroxylase Deficiency CAH	Untested or unknown	Normal for age	Untested or unknown	other hormonal evidence of CAH
Definite	Untested or unknown	Untested or unknown	>135	Untested or unknown	two classic gene mutations or deletions *in trans*	Ambiguous genitalia in 46,XX
Definite	Untested or unknown	Untested or unknown	>135	Untested or unknown	two classic gene mutations or deletions *in trans*	no evidence of salt wasting
Definite	Untested or unknown	Untested or unknown	>135	Untested or unknown	two classic gene mutations or deletions *in trans*	other hormonal evidence of CAH
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Normal for age	two classic gene mutations or deletions *in trans*	Ambiguous genitalia in 46,XX
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Normal for age	two classic gene mutations or deletions *in trans*	no evidence of salt wasting
Definite	Untested or unknown	Untested or unknown	Untested or unknown	Normal for age	two classic gene mutations or deletions *in trans*	other hormonal evidence of CAH

	Probable	1,000 -10,000	Untested or unknown	>135	Untested or unknown	Untested or unknown	Ambiguous genitalia in 46,XX or normal genitalia in 46,XY
	Probable	1,000 -10,000	Untested or unknown	Untested or unknown	Normal for age	Untested or unknown	Ambiguous genitalia in 46,XX or normal genitalia in 46,XY
	Probable	1,000 -10,000	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	no evidence of salt wasting

Alpha thalassemia

Case Definitions Tables

September 29, 2013

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Throughout this document, the following definitions are used:

1. Family studies - both parents with HPLC, IEF outside of newborn period and CBC if microcytosis –low MCH, MCV (assuming iron deficiency has been ruled out and A2 is not elevated, then presumptive alpha thal trait) OR DNA

2. Family history includes reported history of Hgb variant in the family

S Alpha Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC& IEF same sample
Definite	FS+Barts	Untested or unknown	Homozygous S mutation and pathological gene changes found in 1-3 of the alpha genes	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FS+Barts	Homozygous S mutation and pathological gene changes found in 1-3 of the alpha genes	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Homozygous S mutation and pathological gene changes found in 1-3 of the alpha genes	FS + Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FS+Barts	FS+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FS+Barts	Untested or unknown	Untested or unknown	FS+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FS+Barts	Untested or unknown	FS+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FS+Barts x2	Untested or unknown	Untested or unknown	FS+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown

Probable	Untested or unknown	Untested or unknown	Untested or unknown	FS+Barts	Low MCV	Both parents with AS & amount of S <35%; low MCH & ruled out iron deficiency	Untested or unknown	Untested or unknown
Probable	FS+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both parents with AS & amount of S <35%; low MCH & ruled out iron deficiency	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FS+Barts	Untested or unknown	Untested or unknown	Low MCV	Both parents wh AS & amount of S <35%; low MCH & ruled out iron deficiency	Untested or unknown	Untested or unknown

S Alpha Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC& IEF same sample
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FS+Barts	Low MCV	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FS+Barts

C Alpha Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC& IEF same sample
Definite	FC+Barts	Untested or unknown	Known C mutation and Deletion in alpha gene	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FC+Barts	Known C mutation and Deletion in alpha gene	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known C mutation and Deletion in alpha gene	FC+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FC+Barts	FC+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FC+Barts	Untested or unknown	Untested or unknown	FC+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FC+Barts	Untested or unknown	FC+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FC+Barts	Untested or unknown	Untested or unknown	FC+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FC+Barts	Low MCV	Both carriers	Untested or unknown	Untested or unknown
Probable	FC+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers	Untested or unknown	Untested or unknown

Probable	Untested or unknown	FC+Barts	Untested or unknown	Untested or unknown	Low MCV	Both Carriers	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FC+Barts	Low MCV	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FC+Barts

D Alpha Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC& IEF same sample
Definite	FD+Barts	Untested or unknown	Known C mutation and Deletion in alpha gene	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FD+Barts	Known C mutation and Deletion in alpha gene	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known C mutation and Deletion in alpha gene	FD + Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FD+Barts	FD+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FD+Barts	Untested or unknown	Untested or unknown	FD+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FD+Barts	Untested or unknown	FD+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FD+Barts	Low MCV	Both carriers	Untested or unknown	Untested or unknown
Probable	FD+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FD+Barts	Untested or unknown	Untested or unknown	Low MCV	Both Carriers	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FD+Barts	Low MCV	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FD+Barts

O_{Arab} Alpha Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC& IEF same sample
Definite	FO_{ARAB}+Barts	Untested or unknown	Known O_{Arab} mutation and Deletion in alpha gene	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FO_{ARAB}+Barts	Known O_{Arab} mutation and Deletion in alpha gene	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known O_{Arab} mutation and Deletion in alpha gene	FO_{ARAB}+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FO_{ARAB}+Barts	Untested or unknown	FO_{ARAB}+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}TraceAA2	FO_{ARAB}+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}+Barts	Untested or unknown	Untested or unknown	FO_{ARAB}+Barts	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FO_{ARAB}+Barts	Low MCV	Both carriers	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}+Barts	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FO_{ARAB}+Barts	Untested or unknown	Untested or unknown	Low MCV	Both Carriers	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FO_{ARAB}+Barts	Low MCV	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FO_{ARAB}+Barts

3 Deletion Alpha Thalassemia (Hgb H disease)

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA-based testing	NBS result	CBC Results	Family DNA Studies	Family history	HPLC& IEF same sample
Definite	Untested or unknown	≥ 25% Barts by HPLC in newborn period	3 alpha gene defects (deletions or mutations)	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	3 alpha gene defects (deletions or mutations)	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	Barts or Hgb H	Low MCV	Parents with known carriers of 2 gene deletion and 1 gene deletion or point mutation	History of SAB/miscarriage or early termination of pregnancy	Untested or unknown
Probable	Persistent Barts	Untested or unknown	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Persistent Barts	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Elevated Hgb H	Untested or unknown	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Elevated Hgb H	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Nml	Untested or unknown	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Nml	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown

Hgb H Constant Spring (2 alpha gene deletion (cis) plus Constant Spring point mutation (trans))

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family DNA Studies	Family history	HPLC& IEF same sample
Definite	Constant Spring band identified	Untested or unknown	3 alpha gene deletions and Constant spring mutation	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Constant Spring band identified	3 alpha gene deletions and Constant spring mutation	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	3 alpha gene deletions and Constant spring mutation	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Constant Spring band identified	Untested or unknown	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Constant Spring band identified	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	Barts or Hgb H	Low MCV	Parents with known carriers of 2 gene and 1 gene deletion and one with Constant Spring mutation	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Constant Spring band identified	Untested or unknown	Untested or unknown	Untested or unknown	Parents with known carriers of 2 gene and 1 gene deletion and one with Constant Spring mutation	Untested or unknown	Untested or unknown
Probable	Constant Spring band identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Parents with known carriers of 2 gene and 1 gene deletion and one with Constant Spring mutation	Untested or unknown	Untested or unknown
Possible	Nml	Untested or unknown	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Nml	Untested or unknown	Barts or Hgb H	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown

Beta Thalassemia

Case Definitions Tables

September 29, 2013

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The following notes apply throughout these tables:

1. Family studies - both parents with HPLC, IEF and CBC OR DNA
2. Family history includes reported history of Hgb variant in the family
3. Need to exclude iron deficiency if using low MCV as part of criteria

Beta + Thal – (note: need separate samples for column 2 and 3)

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	SBeta + THAL	FSA or FS	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	FSAA_2	Untested or unknown	SBeta + THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FSA with high A_2	SBeta + THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSAA_2	FSA with high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSAA2	Untested or unknown	Untested or unknown	FSA or FS	Untested or unknown	Both carriers (1 each of Beta + THAL and S)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSA with high A_2	Untested or unknown	FSA or FS	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSAA_2	Untested or unknown	Untested or unknown	FSA or FS	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FS	FSA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 each of Beta + THAL and S)	Untested or unknown	Untested or unknown
Probable	FSAA_2 x2	Untested or unknown	Untested or unknown	FSA or FS	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSA	FSA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 each of Beta + THAL and S)	Untested or unknown	Untested or unknown

Beta + Thal – (note: need separate samples for column 2 and 3)

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Probable	Untested or unknown	FSA with high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of Beta + THAL and S)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FSA or FS	Low MCV	Both carriers (1 each of Beta + THAL and S)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	FSA	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of Beta + THAL and S)	Untested or unknown	Untested or unknown
Possible	$FSAA_2$	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of Beta + THAL and S)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FSA or FS	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	$FSAA_2$

E Beta + Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	E Beta + Thal	FEA or FE	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	$FEAA_2$	Untested or unknown	E Beta + Thal	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FEA with high A_2	E Beta + Thal	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FEAA_2$	FEA with high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FEAA_2$	Untested or unknown	Untested or unknown	FEA or FE	Untested or unknown	Both carriers (1 with Beta + thal and one for E)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FEA with high A_2	Untested or unknown	FEA or FE	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FEAA_2$	Untested or unknown	Untested or unknown	FEA or FE	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FE	FEA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with Beta + thal and one for E)	Untested or unknown	Untested or unknown
Probable	$FEAA_2$ x2	Untested or unknown	Untested or unknown	FEA or FE	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FEA	FEA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with Beta + thal and one for E)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FEA with high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for E)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FEA or FE	Low MCV	Both carriers (1 with Beta + thal and one for E)	Untested or unknown	Untested or unknown
Possible	$FEAA_2$	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for E)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FEA or FE	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	$FEAA_2$

D Beta + Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	D Beta + Thal	FDA or FD	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	$FDAA_2$	Untested or unknown	D Beta + THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FDA with high A_2	D Beta + THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FDAA_2$	FDA with high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FDAA_2$	Untested or unknown	Untested or unknown	FDA or FD	Untested or unknown	Both carriers (1 with Beta + thal and one for D)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FDA with high A_2	Untested or unknown	FDA or FD	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FDAA_2$	Untested or unknown	Untested or unknown	FDA or FD	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FD	FDA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with Beta + thal and one for D)	Untested or unknown	Untested or unknown
Probable	$FDAA_2$ x2	Untested or unknown	Untested or unknown	FDA or FD	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown

Probable	FDA	FDA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with Beta + thal and one for D)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FDA with high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for D)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	FDA	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for D)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FDA or FD	Low MCV	Both carriers (1 with Beta + thal and one for D)	Untested or unknown	Untested or unknown
Possible	$FDAA_2$	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for D)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FDA or FD	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	$FDAA_2$

C Beta + Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	C Beta + Thal	FCA or FC	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	$FCAA_2$	Untested or unknown	C Beta + Thal	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FCA with high A_2	C Beta + Thal	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FCAA_2$	FCA with high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FCAA_2$	Untested or unknown	Untested or unknown	FCA or FC	Untested or unknown	Both carriers (1 with Beta + thal and one for C)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FCA with high A_2	Untested or unknown	FCA or FC	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FCAA_2$	Untested or unknown	Untested or unknown	FCA or FC	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCA	FCA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with Beta + thal and one for C)	Untested or unknown	Untested or unknown
Probable	$FCAA_2$ x2	Untested or unknown	Untested or unknown	FCA or FC	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCA	FCA	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with Beta + thal and one for C)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FCA with high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for C)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	FCA	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for C)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FCA or FC	Low MCV	Both carriers (1 with Beta + thal and one for C)	Untested or unknown	Untested or unknown
Possible	$FCAA_2$	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 with Beta + thal and one for C)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FCA or FC	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	$FCAA_2$

O_{Arab} Beta + Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	O_{Arab} Beta + THAL	$FO_{ARAB}A$ or FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	$FO_{ARAB}AA_2$	Untested or unknown	O_{Arab} Beta + THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FO_{ARAB} A with high A_2	O_{Arab} Beta + THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}AA_2$	FO_{ARAB} A with high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}AA_2$ x2	Untested or unknown	Untested or unknown	$FO_{ARAB}A$ or FO_{ARAB}	Untested or unknown	Both carriers (1 Beta + Thal and O_{ARAB})	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FO_{ARAB} A with high A_2	Untested or unknown	$FO_{ARAB}A$ or FO_{ARAB}	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}AA_2$	Untested or unknown	Untested or unknown	$FO_{ARAB}A$ or FO_{ARAB}	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}	$FO_{ARAB}A$	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 Beta + Thal and O_{ARAB})	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}AA_2$ x2	Untested or unknown	Untested or unknown	$FO_{ARAB}A$ or FO_{ARAB}	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}A$	$FO_{ARAB}A$	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 Beta + Thal and O_{ARAB})	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FO_{ARAB} A with high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 Beta + Thal and O_{ARAB})	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	$FO_{ARAB}A$ or FO_{ARAB}	Low MCV	Both carriers (1 Beta + Thal and O_{ARAB})	Untested or unknown	Untested or unknown
Possible	Untested or unknown	FO_{ARAB} A	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 Beta + Thal and O_{ARAB})	Untested or unknown	Untested or unknown
Possible	$FO_{ARAB}AA_2$	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 Beta + Thal and O_{ARAB})	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	$FO_{ARAB}AA_2$	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	$FO_{ARAB}AA_2$

S Beta (0) Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	SBeta 0 THAL	FSA_2 or FS	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	FSA_2 or FS	Untested or unknown	SBeta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FS high A_2	SBeta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSA_2 or FS	FS high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSA_2 or FS	Untested or unknown	Untested or unknown	FSA_2 or FS	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FS high A_2	Untested or unknown	FSA_2 or FS	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FS	FS high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Probable	FSA_2 or FS	Untested or unknown	Untested or unknown	FSA_2 or FS	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FSA_2 or FS	Low MCV	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Probable	FSA_2 or FS x2	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FS high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FSA_2 or FS	Low MCV	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FSA_2

E Beta (0) Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	EBeta 0 THAL	FEA_2 or FE	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	FEA_2 or FE	Untested or unknown	EBeta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FE high A_2	EBeta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FEA_2 or FE	FE high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FEA_2 or FE	Untested or unknown	Untested or unknown	FEA_2 or FE	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FE high A_2	Untested or unknown	FEA_2 or FE	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FE	FE high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Probable	FEA_2	Untested or unknown	Untested or unknown	FEA_2 or FE	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FEA_2 or FE	Low MCV	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Probable	FEA_2 or FE x2	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FE high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta S)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FEA_2 or FE	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FEA_2

D Beta (0) Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	D Beta 0 Thal	FDA_2 or FD	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	FDA_2	Untested or unknown	D Beta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FD high A_2	D Beta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FDA_2	FD high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FDA_2	Untested or unknown	Untested or unknown	FDA_2 or FD	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FD high A_2	Untested or unknown	FDA_2 or FD	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FDA_2 or FD x 2	Untested or unknown	Untested or unknown	FDA_2 or FD	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FDA_2 or FD	Low MCV	Both carriers (1 each of BetaTHAL and Beta D)	Untested or unknown	Untested or unknown
Probable	FDA_2 x2	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta D)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FD high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta D)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FDA_2 or FD	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FDA_2

C Beta (0) Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	C Beta 0 THAL	FCA_2 or FC	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	FCA_2	Untested or unknown	C Beta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FC high A_2	C Beta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCA_2 or FC	FC high A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCA_2 or FC	Untested or unknown	Untested or unknown	FCA_2 or FC	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FC high A_2	Untested or unknown	FCA_2 or FC	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCA_2	Untested or unknown	Untested or unknown	FCA_2 or FC	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FCA_2 or FC	Low MCV	Both carriers (1 each of BetaTHAL and Beta C)	Untested or unknown	Untested or unknown
Probable	FCA_2 or FC x2	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta C)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FC high A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta C)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FCA_2 or FC	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	FCA_2

O_{Arab} Beta (0) Thal

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history	HPLC & IEF same sample
Definite	Untested or unknown	Untested or unknown	O_{Arab} Beta 0 THAL	$FO_{ARAB}A_2$ or FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	$FO_{ARAB}A_2$	Untested or unknown	O_{Arab} Beta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FO_{ARAB} High A_2	O_{Arab} Beta 0 THAL	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}A_2$	FO_{ARAB} High A_2	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}A_2$	Untested or unknown	Untested or unknown	$FO_{ARAB}A_2$ or FO_{ARAB}	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FO_{ARAB} High A_2	Untested or unknown	$FO_{ARAB}A_2$ or FO_{ARAB}	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}A_2$ x2	Untested or unknown	Untested or unknown	$FO_{ARAB}A_2$ or FO_{ARAB}	Low MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	$FO_{ARAB}A_2$ or FO_{ARAB}	Low MCV	Both carriers (1 each of BetaTHAL and Beta O Arab)	Untested or unknown	Untested or unknown
Probable	$FO_{ARAB}A_2$ x2	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta O Arab)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FO_{ARAB} High A_2	Untested or unknown	Untested or unknown	Low MCV	Both carriers (1 each of BetaTHAL and Beta O Arab)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	$FO_{ARAB}A_2$ or FO_{ARAB}	Low MCV	Untested or unknown	Positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Untested or unknown	Untested or unknown	$FO_{ARAB}A_2$

Beta Thal Major or (Homozygous or Heterozygous for 2 Beta Thal mutations) – clinical definition – transfusion dependency defines this – generally manifests after 6mo

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history
Definite	Untested or unknown	Untested or unknown	Homozygous for Point Mutation	F	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	1 Point Mutation and 1 Partial Deletion	F	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	2 Partial Deletions	F	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	2 heterozygous point mutations	F	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	High A_2 (higher than normal)	Untested or unknown	F	Low MCV	Both carriers	Untested or unknown
Probable	F or FA (smaller A than expected)	Untested or unknown	Untested or unknown	F	Low MCV	Both carriers	Untested or unknown
Probable	F or FA (smaller A than expected)	High A_2 (higher than normal)	Untested or unknown	F	Low MCV	Untested or unknown	Untested or unknown
Possible	F	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Both carriers	Untested or unknown
Possible	Untested or unknown	High A_2 (higher than normal)	Untested or unknown	Untested or unknown	Low MCV-	Both Carriers	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	F	Low MCV-	Untested or unknown	positive

HPFH – cannot be confirmed until 6 months of age or older if do not have DNA results

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history
Definite	Untested or unknown	Untested or unknown	Homozygous for Point Mutation	F	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	1 Point Mutation and 1 Deletion	F	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	2 Deletions	F	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	2 heterozygous point mutations	F	Untested or unknown	Untested or unknown	Untested or unknown
Probable	F	F	Untested or unknown	Untested or unknown	Untested or unknown	Both Carriers	Untested or unknown
Probable	F	Untested or unknown	Untested or unknown	F	Untested or unknown	Both Carriers	Untested or unknown
Probable	Untested or unknown	F	Untested or unknown	F	Untested or unknown	Both Carriers	Untested or unknown
Probable	F	Untested or unknown	Untested or unknown	F	Untested or unknown	Both Carriers	Untested or unknown
Possible	F	Untested or unknown	Untested or unknown	F	Normal MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	F	Untested or unknown	F	Normal MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	F	Normal MCV	Both carriers	Untested or unknown
Possible	F	Untested or unknown	Untested or unknown	Untested or unknown	Normal MCV	Both carriers	Untested or unknown
Possible	Untested or unknown	F	Untested or unknown	Untested or unknown	Normal MCV	Both carriers	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	F	Normal MCV	Untested or unknown	Positive

FSHPFH – Cannot be confirmed until older than 6 months of age if do not have DNA results

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history
Definite	Untested or unknown	Untested or unknown	1 mutation With known S mutation	FS	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	1 deletion and known S mutation	FS	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FS	FS	Untested or unknown	Untested or unknown	Untested or unknown	Documented carriers of HPFH and S	Untested or unknown
Possible	Untested or unknown	FS	Untested or unknown	FS	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FS	Untested or unknown	Untested or unknown	FS	Untested or unknown	Documented carriers of HPFH and S	Untested or unknown
Possible	FS	Untested or unknown	Untested or unknown	FS	Normal MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	FS	Untested or unknown	FS	Normal MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FS	Normal MCV	Documented carriers of HPFH and S	Untested or unknown
Possible	FS	Untested or unknown	Untested or unknown	Untested or unknown	Normal MCV	Documented carriers of HPFH and S	Untested or unknown
Possible	Untested or unknown	FS	Untested or unknown	Untested or unknown	Normal MCV	Documented carriers of HPFH and S	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FS	Normal MCV	Untested or unknown	Positive

FO_{ARAB}HPFH – Cannot be confirmed until older than 6 months of age if do not have DNA results

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history
Definite	Untested or unknown	Untested or unknown	1 mutation With known O_{ARAB} mutation	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	1 deletion and known O_{ARAB} mutation	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Documented carriers of HPFH and O_{ARAB}	Untested or unknown
Probable	FO_{ARAB}	Untested or unknown	Untested or unknown	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or Unknown	FO_{ARAB}	Untested or unknown	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}	Untested or unknown	Untested or unknown	FO_{ARAB}	Untested or unknown	Documented carriers of HPFH and O_{ARAB}	Untested or unknown
Possible	FO_{ARAB}	Untested or unknown	Untested or unknown	FO_{ARAB}	Normal MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	FO_{ARAB}	Untested or unknown	FO_{ARAB}	Normal MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FO_{ARAB}	Normal MCV	Documented carriers of HPFH and O_{ARAB}	Untested or unknown
Possible	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Normal MCV	Documented carriers of HPFH and O_{ARAB}	Untested or unknown
Possible	Untested or unknown	FO_{ARAB}	Untested or unknown	Untested or unknown	Normal MCV	Documented carriers of HPFH and O_{ARAB}	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FO_{ARAB}	Normal MCV	Untested or unknown	Positive

FCHPFH – Cannot be confirmed until older than 6 months of age if do not have DNA results

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history
Definite	Untested or unknown	Untested or unknown	1 mutation With known C mutation	FC	Low MCV	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	1 deletion and known C mutation	FC	Low MCV	Untested or unknown	Untested or unknown
Probable	FC	FC	Untested or unknown	Untested or unknown	Low MCV	Documented carriers of HPFH and C	Untested or unknown
Probable	FC	Untested or unknown	Untested or unknown	FC	Low MCV	Documented carriers of HPFH and C	Untested or unknown
Possible	Untested or unknown	FC	Untested or unknown	FC	Low MCV	Untested or unknown	Untested or unknown
Possible	FC	Untested or unknown	Untested or unknown	FC	Low MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FC	Low MCV	Documented carriers of HPFH and C	Untested or unknown
Possible	FC	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Documented carriers of HPFH and C	Untested or unknown
Possible	Untested or unknown	FC	Untested or unknown	Untested or unknown	Low MCV	Documented carriers of HPFH and C	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FC	Low MCV	Untested or unknown	Positive

FEHPFH – Cannot be confirmed until older than 6 months of age if do not have DNA results

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA sequencing and deletion	NBS result	CBC Results	Family Studies	Family history
Definite	Untested or unknown	Untested or unknown	1 deletion and known E mutation	FE	Low MCV	Untested or unknown	Untested or unknown
Probable	FE	FE	Untested or unknown	Untested or unknown	Low MCV	Documented carriers of HPFH and E	Untested or unknown
Probable	FE	Untested or unknown	Untested or unknown	FE	Low MCV	Documented carriers of HPFH and E	Untested or unknown
Probable	Untested or unknown	FE	Untested or unknown	FE	Low MCV	Documented carriers of HPFH and E	Untested or unknown
Possible	FE	Untested or unknown	Untested or unknown	FE	Low MCV	Untested or unknown	Untested or unknown
Possible	FE	Untested or unknown	Untested or unknown	FE	Low MCV	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FE	Low MCV	Documented carriers of HPFH and E	Untested or unknown
Possible	FE	Untested or unknown	Untested or unknown	Untested or unknown	Low MCV	Documented carriers of HPFH and E	Untested or unknown
Possible	Untested or unknown	FE	Untested or unknown	Untested or unknown	Low MCV	Documented carriers of HPFH and E	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FE	Low MCV	Untested or unknown	Positive

C and E will not have normal MCV with HPFH- do not reference MCV

Sickle Cell Diseases

Case Definitions Tables

September 29, 2013

Definitions created by panel of experts between June 2011 and September 2013. This project was funded in part by Cooperative Agreement # U22MC24078 from the Health Resources and Services Administration (HRSA).

Throughout this document, the following definitions are used:

1. Family studies - both parents with HPLC, IEF and CBC
2. Family history includes reported history of Hgb variant in the family

SC Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FSC	Untested or unknown	Known C and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FSC	Known C and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known C and known S mutation identified	FSC	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known C and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	FSC
Probable	FSC	FSC	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSC	Untested or unknown	Untested or unknown	FSC	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSC	Untested or unknown	FSC	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FSC	Both carriers (1 with C mutation and other with S mutation)	Untested or unknown	Untested or unknown
Probable	FSC	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with C mutation and other with S mutation)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSC	Untested or unknown	Untested or unknown	Both carriers (1 with C mutation and other with S mutation)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FSC	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FSC

SD Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FSD	Untested or unknown	Known D and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FSD	Known D and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known D and known S mutation identified	FSD	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known D and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	FSD
Probable	FSD	FSD	Untested or unknown	Untested or	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSD	Untested or	Untested or unknown	FSD	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSD	Untested or unknown	FSD	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FSD	Both carriers (1 with known S mutation and 1 with known D mutation)	Untested or unknown	Untested or unknown
Probable	FSD	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with known S mutation and 1 with known D)	Untested or unknown	Untested or unknown

SD Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Probable	Untested or unknown	FSD	Untested or unknown	Untested or unknown	Both carriers (1 with known S mutation and 1 with known D)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FSD	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FSD

SE Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FSE	Untested or unknown	Known E and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FSE	Known E and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known E and known S mutation identified	FSE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSE	FSE	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSE	Untested or unknown	Untested or unknown	FSE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSE	Untested or unknown	FSE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FSE	Both carriers (1 with known S mutation and 1 with known E)	Untested or unknown	Untested or unknown
Probable	FSE	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with known S mutation and 1 with knownE)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSE	Untested or unknown	Untested or unknown	Both carriers (1 with known S mutation and 1 with known E)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FSE	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FSE

SO_{Arab} Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FSO_{ARAB}	Untested or unknown	Known O_{ARAB} and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FSO_{ARAB}	Known O_{ARAB} and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known O_{ARAB} and known S mutation identified	FSO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSO_{ARAB}	FSO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FSO_{ARAB}	Untested or unknown	Untested or unknown	FSO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSO_{ARAB}	Untested or unknown	FSO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FSO_{ARAB}	Both carriers (1 with known S mutation and 1 with known O_{ARAB})	Untested or unknown	Untested or unknown
Probable	FSO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with known S mutation and 1 with known O_{ARAB})	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FSO_{ARAB}	Untested or unknown	Untested or unknown	Both carriers (1 with known S mutation and 1 with known O_{ARAB})	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FSO_{ARAB}	Untested or unknown	positive	Untested or unknown
Poss ible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FSO_{ARAB}

CD Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FCD	Untested or unknown	Known C and known D mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FCD	Known C and known D mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known C and known D mutation identified	FCD	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCD	FCD	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCD	Untested or unknown	Untested or unknown	FCD	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FCD	Untested or unknown	FCD	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FCD	Both carriers (1 with D and 1 with E)	Untested or unknown	Untested or unknown
Probable	FCD	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 with D and 1 with E)	Untested or unknown	Untested or unknown

CD Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Probable	Untested or unknown	FCD	Untested or unknown	Untested or unknown	Both carriers (1 with D and 1 with E)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FCD	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FCD

CE Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FCE	Untested or unknown	Known C and known E mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FCE	Known C and known E mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known C and known E mutation identified	FCE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCE	FCE	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCE	Untested or unknown	Untested or unknown	FCE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FCE	Untested or unknown	FCE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FCE	Both carriers (1 with C and 1 with E)	Untested or unknown	Untested or unknown
Probable	FCE	Untested or unknown	Untested or unknown	Untested or	Both carriers (1 with C and 1 with E)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FCE	Untested or unknown	Untested or	Both carriers (1 with C and 1 with E)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FCE	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or	Untested or unknown	Untested or unknown	FCE

CO_{Arab} Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FCO_{ARAB}	Untested or unknown	Known C and known O_{ARAB} mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FCO_{ARAB}	Known C and known O_{ARAB} mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known C and known O_{ARAB} mutation identified	FCO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCO_{ARAB}	FCO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FCO_{ARAB}	Untested or unknown	Untested or unknown	FCO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FCO_{ARAB}	Untested or unknown	FCO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FCO_{ARAB}	Both carriers (1 carrier C and 1 carrier O_{ARAB})	Untested or unknown	Untested or unknown
Probable	FCO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 carrier C and 1 carrier O_{ARAB})	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FCO_{ARAB}	Untested or unknown	Untested or unknown	Both carriers (1 carrier C and 1 carrier O_{ARAB})	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FCO_{ARAB}	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FCO_{ARAB}

DE Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FDE	Untested or unknown	Known D and known E mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FDE	Known D and known E mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known D and known E mutation identified	FDE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FDE	FDE	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FDE	Untested or unknown	Untested or unknown	FDE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FDE	Untested or unknown	FDE	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FDE	Both carriers (1 carrier E and 1 carrier D)	Untested or unknown	Untested or unknown
Probable	FDE	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 carrier E and 1 carrier D)	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FDE	Untested or unknown	Untested or unknown	Both carriers (1 carrier E and 1 carrier D)	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FDE	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FDE

DO_{Arab} Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	Family Studies	Family history	HPLC& IEF same sample
Definite	FDO_{ARAB}	Untested or unknown	Known O_{ARAB} and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FDO_{ARAB}	Known O_{ARAB} and known S mutation identified	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	Known O_{ARAB} and known S mutation identified	FDO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FDO_{ARAB}	FDO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown
Probable	FDO_{ARAB}	Untested or unknown	Untested or unknown	FDO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FDO_{ARAB}	Untested or unknown	FDO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	Untested or unknown	FDO_{ARAB}	Both carriers (1 carrier C and 1 carrier O_{ARAB})	Untested or unknown	Untested or unknown
Probable	FDO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers (1 carrier C and 1 carrier O_{ARAB})	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FDO_{ARAB}	Untested or unknown	Untested or unknown	Both carriers (1 carrier C and 1 carrier O_{ARAB})	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FDO_{ARAB}	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	Untested or unknown	FDO_{ARAB}

SS Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA-	NBS result	CBC	Family Studies	Family history	Hbg testing (Electrophoresis or HPLC) on family members
Definite	FS	Untested or unknown	SS	Untested or unknown	Untested or unknown	Both carriers S	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FS	SS	Untested or unknown	Untested or unknown	Both carriers S	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	SS	FS	Untested or unknown	Both carriers S	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	SS	Untested or unknown	Untested or unknown	Both carriers S		
Probable	FS	Untested or unknown	Untested or unknown	FS	Nml- high MCV	Untested or unknown	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FS	Untested or unknown	FS	Untested or unknown	Both carriers S	Untested or unknown	Untested or unknown
Probable	FS	Untested or unknown	Untested or unknown	FS	Untested or unknown	Both carriers S	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FS	Nml- high MCV	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FS	Untested or unknown	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FS	Untested or unknown	Untested or unknown	Untested or unknown	positive

CC Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA	NBS result	CBC	Family Studies	Family history	Hbg testing (Electrophoresis or HPLC) on family members
Definite	Untested or unknown	FC	CC	Untested or unknown	Nml MCV	Both carriers C	Untested or unknown	Untested or unknown
Definite	FC	Untested or unknown	CC	Untested or unknown	Nml MCV	Both carriers C	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	CC	FC	Nml MCV	Both carriers C	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	CC	Untested or unknown	Untested or unknown	Both Carriers C		
Probable	Untested or unknown	FC	Untested or unknown	FC	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Probable	FC	FC	Untested or unknown	Untested or unknown	Untested or unknown	Both Carriers C	Untested or unknown	Untested or unknown
Probable	FC	Untested or unknown	Untested or unknown	FC	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FC	Nml MCV	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FC	Untested or unknown	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FC	Untested or unknown	Untested or unknown	Untested or unknown	positive

EE Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA- no deletion/duplication analysis	NBS result	CBC	Family Studies	Family history	Hbg testing (Electrophoresis or HPLC) on family members
Definite	FE	Untested or unknown	EE	Untested or unknown	Nml MCV	Both carriers E	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FE	EE	Untested or unknown	Nml MCV	Both carriers E	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	EE	FE	Nml MCV	Both carriers E	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	EE	Untested or unknown	Untested or unknown	Both Carriers E	Untested or unknown	Untested or unknown
Probable	FE	FE	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers E	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FE	Untested or unknown	FE	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Probable	FE	Untested or unknown	Untested or unknown	FE	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FE	Nml MCV	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FE	Untested or unknown	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FE	Untested or unknown	Untested or unknown	Untested or unknown	positive

DD Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA-	NBS result	CBC	Family Studies	Family history	Hbg testing (Electrophoresis or HPLC) on family members
Definite	FD	Untested or unknown	DD	Untested or unknown	Nml MCV	Both carriers D	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FD	DD	Untested or unknown	Nml MCV	Both carriers D	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	DD	FD	Nml MCV	Both carriers D	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	DD	Untested or unknown	Untested or unknown	Both Carriers D	Untested or unknown	Untested or unknown
Probable	FD	FD	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers D	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FD	Untested or unknown	FD	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Probable	FD	Untested or unknown	Untested or unknown	FD	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FD	Nml MCV	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FD	Untested or unknown	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FD	Untested or unknown	Untested or unknown	Untested or unknown	positive

Homozygous O_{Arab} Disease

Category	Qualitative (IEF or HPLC)	Quantitative (HPLC or electrophoresis)	DNA-	NBS result	CBC	Family Studies	Family history	Hbg testing (Electrophoresis or HPLC) on family members
Definite	FO_{ARAB}	Untested or unknown	$O_{ARAB}O_{ARAB}$	Untested or unknown	Nml MCV	Both carriers O_{ARAB}	Untested or unknown	Untested or unknown
Definite	Untested or unknown	FO_{ARAB}	$O_{ARAB}O_{ARAB}$	Untested or unknown	Nml MCV	Both carriers O_{ARAB}	Untested or unknown	Untested or unknown
Definite	Untested or unknown	Untested or unknown	$O_{ARAB}O_{ARAB}$	FO_{ARAB}	Nml MCV	Both carriers O_{ARAB}	Untested or unknown	Untested or unknown
Probable	Untested or unknown	Untested or unknown	$O_{ARAB}O_{ARAB}$	Untested or unknown	Untested or unknown	Both Carriers O_{ARAB}	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	Both carriers O_{ARAB}	Untested or unknown	Untested or unknown
Probable	Untested or unknown	FO_{ARAB}	Untested or unknown	FO_{ARAB}	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Probable	FO_{ARAB}	Untested or unknown	Untested or unknown	FO_{ARAB}	Untested or unknown	Both carriers	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FO_{ARAB}	Nml MCV	Untested or unknown	Untested or unknown	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FO_{ARAB}	Untested or unknown	Untested or unknown	positive	Untested or unknown
Possible	Untested or unknown	Untested or unknown	Untested or unknown	FO_{ARAB}	Untested or unknown	Untested or unknown	Untested or unknown	positive

Cystic Fibrosis

Case Definitions Tables

September 29, 2013

Definitions created by panel of experts between June 2011 and September 2013. This project was funded in part by Cooperative Agreement # U22MC24078 from the Health Resources and Services Administration (HRSA).

Note: CF Disease Causing Mutations should be confirmed on CFTR2 (www.cftr2.org)

CF Disease Causing Mutations should be confirmed on CFTR2 (www.cftr2.org).

Typical CF

Category	Classification	Clinical	Sweat Chloride	Non Newborn Screen Molecular	Newborn Screen Molecular	NBS Result
Typical CF	Definite		>=60 mmol/L (regardless of age)	*Not available or not done*	2 CF disease-causing mutations	
	Definite		>=60 mmol/L (regardless of age)	2 CF disease-causing mutations	*Not available or not done*	
	Definite		No valid sweat chloride result available	2 CF disease-causing mutations	2 CF disease-causing mutations	
	Definite	No known medical condition associated with false positive sweat chloride	TWO results >=60 mmol/L (regardless of age, two independent results from separate days)	*Not available or not done*	*Not available or not done*	
	Definite		<60 mmol/L	2 CF disease-causing mutations ***and*** 1 or both have been shown to have lower chlorides (see CFTR2)	2 CF disease-causing mutations ***and*** 1 or both have been previously shown to have lower chlorides, (see CFTR2)	
	Probable		No valid sweat chloride result available	*Not available or not done*	2 CF-causing mutations	
	Probable		No valid sweat chloride result available	2 CF-causing mutations	*Not available or not done*	
	Probable		>=60 mmol/L (single test, regardless of age)	*Not available or not done*	2 Mutations of varying clinical significance	
	Probable		>=60 mmol/L (single test, regardless of age)	*Not available or not done*	2 Mutations of unknown clinical significance	
	Probable		>=60 mmol/L (single test, regardless of age)	2 Mutations of varying clinical consequence	*Not available or not done*	
	Probable		>=60 mmol/L (single test, regardless of age)	2 Mutations of unknown clinical significance	*Not available or not done*	
	Probable		<60 mmol/L	2 CF disease-causing mutations ***and*** 1 or both have been previously shown to have lower chlorides	*Not available or not done*	
	Probable		<60 mmol/L	*Not available or not done*	2 CF disease-causing mutations ***and*** 1 or both have been previously shown to have lower chlorides,	

CF Disease Causing Mutations should be confirmed on CFTR2 (www.cftr2.org).

Typical CF

Category	Classification	Clinical	Sweat Chloride	Non Newborn Screen Molecular	Newborn Screen Molecular	NBS Result
Typical CF	Possible		No valid sweat chloride result available	2 CF disease-causing mutations CF-causing mutations not yet shown to be *in trans*	*Not available or not done*	
Typical CF	Possible		No valid sweat chloride result available	*Not available or not done*	2 CF disease-causing mutations CF-causing	
CR MS	Definite		<30 if <6mos, <40 if ≥6 mos On 2 occasions	1 CF disease-causing mutation **and** 1 Mutation of varying clinical consequence *in trans*		Elevated IRT
CR MS	Definite		<30 if <6mos, <40 if >6 mos On 2 occasions	1 CF disease-causing mutation **and** 1 Mutation of unknown significance		Elevated IRT
CR MS	Definite		30-59 (age<6 mos) On 2 occasions		1 CF disease-causing mutation **and** 1 Mutation of unknown significance	Elevated IRT
CR MS	Definite		40 -59 (age≥6 mos) On 2 occasions		1 CF disease-causing mutation **and** 1 Mutation of varying clinical consequence	Elevated IRT
CR MS	Definite		30-59 (age<6 mos) On 2 occasions			Elevated IRT
CR MS	Definite		40 -59 (age>6 mos) On 2 occasions			Elevated IRT

CF Disease Causing Mutations should be confirmed on CFTR2 (www.cftr2.org).

Typical CF

Category	Classification	Clinical	Sweat Chloride	Non Newborn Screen Molecular	Newborn Screen Molecular	NBS Result
CRD	Definite	CBAVD, recurrent pancreatitis, nasal polyposis, infertility and focal biliary cirrhosis with portal hypertension	30-59 (age<6 mos) On 2 occasions	1 CF disease-causing mutation **and** 1 Mutation of unknown significance		
	Definite	CBAVD, recurrent pancreatitis, nasal polyposis, infertility and focal biliary cirrhosis with portal hypertension	30-59 (age<6 mos) On 2 occasions	1 CF disease-causing mutation **and** 1 Mutation of varying clinical consequence		

Severe Combined Immunodeficiency

Case Definitions Tables

May, 2018

Definitions created by panel of experts between June 2011 and September 2013. This project was funded in part by Cooperative Agreement # U22MC24078 from the Health Resources and Services Administration (HRSA).

1. Primary targets of NBS
    a. Typical SCID
    b. Leaky SCID
    c. Omenn Syndrome
2. Secondary targets of NBS
    a. Syndromes with variable immune defects, with some cases having significantly low T-cell numbers
    b. Secondary T-cell lymphopenia
    c. Idiopathic T-cell lymphopenia

Typical SCID

Classification: Typical SCID	CD3 T cells/μL	Proliferation to PHA	Maternal engraftment Y/N	Molecular testing	Clinical Presentation
1. Definite	<300 autologous T Cells, undetectable or very few naïve T cells	<10% of normal	Yes	Consistent with SCID^	
2. Definite	<300 autologous T Cells, undetectable or very few naïve T cells	<10% of normal	Yes	Unknown or not done	
3. Definite	<300 autologous T Cells, undetectable or very few naïve T cells	Unknown or any	Yes	Consistent with SCID^	
4. Definite	Any number	<10% of normal	Yes	Consistent with SCID^	
5. Definite	<300 autologous T Cells, undetectable or very few naïve T cells	<10% of normal	No	Consistent with SCID^	
6. Probable	<300 autologous T Cells, undetectable or very few naïve T cells	<10% of normal	No	Unknown or not done	

7. Probable	Any number	<10% of normal	No	Consistent with SCID^	
8. Probable	Any number	<10% of normal	Yes	Unknown or not done	
9. Probable	Any number	Unknown or any	Yes	None or inconclusive	
10. Probable	Any number	Unknown or any	Yes	Consistent with SCID^	
11. Possible	<300 autologous T Cells, undetectable or very few naïve T cells	<10% of normal	Untested or unknown	Untested or unknown	Untested or unknown
12. Possible	<300 autologous T Cells, undetectable or very few naïve T cells	Unknown or any	No	Unknown or not done	
13. Possible	<300 autologous T Cells, undetectable or very few naïve T cells	Unknown or any	No	Consistent with SCID^	
14. Probable	<300 autologous T Cells, undetectable or very few naïve T cells	Unknown or any	Yes	Unknown or not done	
15. Possible	Any number	Unknown or any	No	Consistent with SCID^	
16. Possible	Any number	<10% of normal	No	None or inconclusive	
17. Uncertain	Any number	Unknown or any	No	Unknown or not done	

^ Consistent with SCID: Two pathogenic variants in a known SCID gene; pathogenic variant in SCID gene on X chromosome in a male; ruled out 22q11 deletion; ruled out heterozygous TBX1 variants; ruled out homozygous or compound heterozygous FOXN1 mutations

Leaky SCID

Classification: Leaky SCID	CD3 T cells/μL	Proliferation	Maternal engraftment Y/N	Molecular testing	Clinical Presentation
1. Definite	300-1500, few naïve T cells, oligoclonal T cells or poor T cell diversity	10-50% normal PHA	No	Unknown or not done	
2. Definite	300-1500, few naïve T cells	10-50% normal PHA	No	Consistent with SCID^	
3. Possible	300-1500, few naïve T cells	Unknown or any	No	Unknown or not done	
4. Definite	300-1500, few naïve T cells	Unknown or any	No	Consistent with SCID^	
5. Possible	Any number	10-30% normal PHA *or* Absent to Candida/TT	No	Unknown or not done	
6. Definite	Any number	10-30% normal PHA *or* Absent to Candida/TT	No	Consistent with SCID^	

^^ Consistent with Leaky SCID: Two pathogenic variants in a known SCID gene known to be associated with leaky SCID (previously reported or in a gene previously associated with a combined immune deficiency) or one pathogenic variant in SCID gene on X chromosome in a male; ruled out 22q11 deletion; ruled out heterozygous TBX1 variants; ruled out homozygous or compound heterozygous FOXN1 mutations

Omenn Syndrome

Classification: Omenn syndrome	CD3 T cells/μL	Proliferation to PHA	Maternal engraftment Y/N	Molecular testing	Clinical Presentation
1. Definite	>80%CD45RO+	10-50%normal	No	Consistent with OS/SCID^^	Consistent with OS**
2. Definite	>80%CD45RO+	10-50%normal	No	Untested or unknown	Consistent with OS**
3. Definite	>80%CD45RO+	10-50%normal	No	No variant reported, ruled out 22q11 and FOXN1	Consistent with OS**
4. Probable	>80%CD45RO+	Untested or unknown	No	Consistent with OS/SCID^^	Consistent with OS**
5. Probable	>80%CD45RO+	10-50%normal	Unknown	Untested or unknown	Consistent with OS**
6. Uncertain	>80%CD45RO+	Untested or Unknown	Untested or Unknown	Untested or Unknown	Consistent with OS**

** Clinical presentation may include Erythroderma with biopsy showing T cell infiltrate; hepatomegaly, splenomegaly or both; adenopathy, eosinophilia, elevated levels of serum IgE antibody

^^ Consistent with OS/SCID: Two pathogenic variants in a SCID gene known to be associated with leaky SCID (previously reported or in a gene previously associated with a combined immune deficiency) or one pathogenic variant in SCID gene on X chromosome in a male**;** ruled out 22q11 deletion; ruled out heterozygous TBX1 variants; ruled out homozygous or compound heterozygous FOXN1 mutations

Non-SCID conditions associated with SCID NBS

Classification	Findings
Syndromes with low T-cell numbers	Recognized genetic syndrome that includes variable immune defects, with some cases having significantly low T-cell numbers (DiGeorge syndrome, FOXN1, CHARGE syndrome, Trisomy 21, Jacobsen syndrome, RAC2 defect, DOCK8 deficiency, Ataxia Telangiectasia, VACTERL association, Barth syndrome, TAR syndrome, Ectrodactyly Ectodermal Dysplasia syndrome, Cartilage Hair Hypoplasia, others)
Secondary T-cell lymphopenia	Congenital malformation or disease process without an intrinsic defect in production of circulating T-cells (e.g. congenital heart disease with vascular leak, hydrops, gastroschisis, chylothorax, intestinal lymphangiectasia, others)
Preterm birth alone	Preterm birth and low birth weight, with low T cell numbers early in life that normalize over time
Idiopathic T-cell lymphopenia (formerly called Variant SCID)	Persistently low T cell numbers for over 3 months without recognized cause

In all of these other conditions there is 1) no maternal engraftment, 2) the T cells are largely naïve, 3) PHA proliferation is usually normal.

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Pompe Disease

Case Definitions Tables

May, 2018

Definitions created by panel of experts between June 2011 and September 2013. This project was funded in part by Cooperative Agreement # U22MC24078 from the Health Resources and Services Administration (HRSA).

Pompe Disease

				Enzyme activity				
Pompe Disease	Classification	Disorder	Mutation Status	Blood (not DBS sample)	Skin/Muscle testing	Cardiac Involvement consistent with Pompe	Lab Findings	Clinical Findings
	Definite	Infantile Onset Pompe Disease	Allele 1 –pathogenic and associated with infantile onset and Allele 2 – pathogenic and associated with infantile onset	Within lab known affected range for infantile onset (IO)	Not done or positive skin or muscle bx	Positive findings on Chest X-ray/EKG/ECHO in newborn period	Unknown/Not Done	
	Definite	Infantile Onset Pompe Disease	Unknown or not done	Within lab known affected range for IO	Not done or positive skin or muscle bx	Positive findings on Chest X-ray/EKG/ECHO in newborn period	Elevated CK/AST/ALT/ LDH/Urine Hex4	
	Definite	Infantile Onset Pompe Disease	Allele 1 – pathogenic and associated with infantile onset, 1 novel variant that is likely pathogenic	Within lab known affected range for IO	Not done or positive skin or muscle bx	Positive findings on Chest X-ray/EKG/ECHO in newborn period	Elevated CK/AST/ALT/ LDH/Urine Hex4	
	Definite	Infantile Onset Pompe Disease	Allele 1 – pathogenic and associated with infantile onset and Allele 2 – pathogenic and associated with infantile onset	Within lab known affected range for IO	Not done or positive skin or muscle bx	Positive findings on Chest X-ray/EKG/ECHO in newborn period	Elevated CK/AST/ALT/ LDH/Urine Hex4	
	Definite	Infantile Onset Pompe Disease	1 pathogenic* or likely pathogenic variant, with deletion or duplication consistent with infantile onset	Within lab known affected range for IO	Not done	Positive findings on Chest X-ray/EKG/ECHO	Elevated CK/AST/ALT/ LDH/Urine Hex4	
	Definite	Infantile Onset Pompe Disease	Allele 1 – pathogenic and associated with infantile onset and Allele 2 – pathogenic and associated with non-classical disease, or variant of uncertain significance	Low (above affected range, for IO, may or may not be in late-onset (LO) range but should not be	positive skin or muscle bx	Positive findings on Chest X-ray/EKG/ECHO in newborn period	Elevated CK/AST/ALT/ LDH/Urine Hex4	

				above LO range))				
	Probable	Infantile Onset Pompe Disease	Allele 1 – pathogenic and associated with infantile onset and Allele 2 – pathogenic and associated with non-classical disease, or variant of uncertain significance)	Within lab known affected range for IO	Unknown/not done	Positive findings on Chest X-ray/EKG/ECHO	Unknown/not done	
	Probable	Infantile Onset Pompe Disease	1 pathogenic* or likely pathogenic variant, no other variants found, dup/del testing not done or not known	Within lab known affected range for IO	Unknown/not done	Positive findings on Chest X-ray/EKG/ECHO	Elevated CK/AST/ALT/ LDH/Urine Hex4	
	Definite	Late Onset Pompe Disease	Allele 1 – pathogenic and Allele 2 – pathogenic and associated with non-classical disease, or variant of uncertain significance)	Within lab known affected range for LO	Unknown/not done	No	Elevated CK/AST/ALT/ LDH/Urine Hex4	Symptoms present after 1 year of age and documented by specialists. PH program continued to collect data through the development of symptoms**
	Definite	Late Onset Pompe Disease	Allele 1 – pathogenic and Allele 2 – pathogenic and associated with non-classical disease, or variant of uncertain significance)	Within lab known affected range for LO	Unknown/not done	No	Elevated CK/AST/ALT/ LDH/Urine Hex4	Symptoms present before 1 year of age but no cardiac involvement
	Probable	Late Onset Pompe Disease	Allele 1 – pathogenic and associated with infantile onset and Allele 2 – pathogenic associated with non-classical disease, or variant of uncertain significance)	Within lab known affected range for LO	Unknown/not done	No	Elevated CK/AST/ALT/ LDH/Urine Hex4	Unknown or not reported to PH to program by the end of follow-up
	Possible	Late Onset Pompe Disease	Allele 1 – pathogenic* and associated with infantile	Low (above affected	Unknown/not done	No	Not present	

			onset and Allele 2 – pathogenic*)	range,for LO not normal)				
	Possible	Late Onset Pompe Disease	Allele 1 – pathogenic* and associated with infantile onset), no other variants detected; Duplication/deletion testing not completed or unknown	Within lab known affected range for LO	Unknown/not done	No	Not present	
	Definite	Late Onset Pompe Disease	Allele 1 – pathogenic* and associated with infantile onset), no other variants detected; Duplication/deletion testing not completed or unknown	Within lab known affected range for LO	Unknown/not done	No	Elevated CK/AST/ALT/ LDH/Urine Hex4	Symptoms present after 1 year of age and documented by specialists. PH program continued to collect data through the development of symptoms**
	Possible	Late Onset Pompe Disease	1 pathogenic* or likely pathogenic variant, no other variant found	Within lab known affected range	Unknown/not done	No	Elevated CK/AST/ALT/ LDH/Urine Hex4	
	Possible	Late Onset Pompe Disease	1 pathogenic* or likely pathogenic variant, no other variants found	Within lab known affected range	Unknown/not done	No	Not present	

* Pathogenic: classified as pathogenic or likely pathogenic by ACMG Guidelines (2015)

** Clinical symptoms consistent with Pompe Disease: progressive muscle weakness, need for respiratory assistance, swaying gait or waddle, Lordosis, kyphosis, or scoliosis.

MPS I

Case Definitions Tables

May, 2018

Definitions created by panel of experts between June 2011 and September 2013. This project was funded in part by Cooperative Agreement # U22MC24078 from the Health Resources and Services Administration (HRSA).

MPS I

	Classification	Disorder	Mutation Status	Enzyme Activity	Urine GAGS	Clinical Symptoms/Lab Findings
MPS I	Definite	MPS I – severe	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – pathogenic and associated with severe disease #	Within lab known affected range	Elevated	
	Definite	MPS I - severity not determined	Allele 1 – pathogenic* or likely pathogenic and Allele 2 – variant with uncertain significance	Within lab known affected range	Elevated	
	Definite	MPS I – severity not determined	Not Done/unknown	Within lab known affected range	Elevated	
	Probable	MPS I – severe	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – pathogenic* and associated with severe disease #	Within lab known affected range	Not done/UNKNOWN	
	Probable	MPS I – severe	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – pathogenic* and associated with severe disease #	Unknown	Not done/UNKNOWN	
	Definite	MPS I Attenuated	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – variant known to be associated with ATTENUATED Disease #	Within lab known affected range	Elevated	Symptoms present and documented by specialists. PH program continued to collect data through the development of symptoms**
	Definite	MPS I Attenuated	Allele 1 – variant known to be associated with ATTENUATED Disease and Allele 2 – variant	Within lab known affected range	Elevated	

			known to be associated with ATTENUATED Disease #			
	Probable	MPS I Attenuated	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – variant known to be associated with ATTENUATED Disease #	Unknown/Not Done	Unknown/Not Done	Symptoms present and documented by specialists. PH program continued to collect data through the development of symptoms**
	Possible	MPS I Attenuated	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – variant known to be associated with ATTENUATED Disease #	Within lab known affected range	Not done/UNKNOWN	UNKNOWN
	Possible	MPS I Attenuated	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – variant known to be associated with ATTENUATED Disease #	Unknown	Not done/UNKNOWN	
	Possible	MPS I - Severity not determined	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – variant of unknown significance	Unknown	Not done/UNKNOWN	Symptoms present and documented by specialists. PH program continued to collect data through the development of symptoms**
	Possible	MPS I Attenuated	Allele 1 – pathogenic* and associated with severe disease and Allele 2 – variant of unknown significance	Unknown	Not done/UNKNOWN	No symptoms by the time the PH Program closes follow-up (either due to child being lost to follow-up OR program policy on follow-up time

* Pathogenic: Reported in cases known to have severe cases previously.

All reports of two variants determined to be disease causing are assumed to bin *in trans, and appropriate testing was completed as necessary*

** Clinical symptoms consistent with MPS-I include: Hepatosplenomegaly, Coarse facial features, Hydrocephalus, Skeletal deformities (dysostosis multiplex), Corneal clouding, Large tongue, Prominent forehead, Joint stiffness, Short stature, frequent ear infections and hearing loss, hernia

X-ALD Newborn Screening

Case Definitions Tables

September 2018

Definitions created by a panel of experts is supported by the Health Resources and Services Administration (HRSA) under Cooperative Agreement # UG9MC30369 New Disorders Implementation Project.

X-ALD

In Males:

	Category	Plasma VLCFA	Clinical Symptoms	Plasmalogen	Mutation analysis	Family History
X-linked Adrenoleukodystrophy	Definite	Elevated^	Not present	Untested or unknown	Pathogenic Variant in *ABCD1* gene	
	Definite	Elevated^	Not present	Normal	Deletion/duplication identified in *ABCD1* gene	
	Definite	Elevated^	Not present	Normal	No mutation on sequencing, deletion/duplication not done	Family history or family VLCFA studies suggestive of X-linked ALD
	Definite	Elevated^	Not present	Normal	Variant of uncertain significance in *ACBD1* gene	Family history or family VLCFA studies suggestive of X-linked ALD
	Possible	Elevated^	Not present	Normal	Variant of uncertain significance in *ACBD1* gene	
	Possible	Elevated^	Not present	Normal	No mutation on sequencing, deletion/duplication not done; Rule out other disorders of peroxisomal beta oxidation	
	Possible	Elevated^	Not present	Normal	Untested or unknown	
	Probable	Not available	Not available	Not available	Pathogenic Variant in *ABCD1* gene	
	Possible	Not available	Not present	Not available	Variant of uncertain significance in *ACBD1* gene	Family history or family VLCFA studies suggestive of X-linked ALD#

^ In the pathogenic range

Family history may include multiple relatives consistent with X-linked transmission as determined by clinical specialist: Maternal grandfather, maternal aunts, mother

contiguous ABCD1 DXS1357E deletion syndrome (CADDS)	Definite	Elevated^	Present**	Normal	Deletion identified in *ABCD1* and *DXS1357E*	

^ In the pathogenic range

** Symptoms may include: neonatal hypotonia, neonatal seizures, liver disease, neonatal cholestasis, sensorineural deafness

In Females:

X-linked Adrenoleukodystrophy	Category	Diagnosis	Plasma VLCFA	Plasmalogen	Mutation analysis	Fibroblast studies	Additional Comments
	Definite	Carrier Female	Normal	Normal	Pathogenic variant *ABCD1* gene	Untested or unknown	
	Definite	Carrier Female	Elevated^	Normal	Pathogenic variant *ABCD1* gene	Untested or unknown	
	Possible	Carrier Female	Elevated^	Not done/unknown	Not done/unknown		
	Possible	Carrier Female	Not done/unknown	Not done/unknown	Not done/unknown	Not done/unknown	Family history or family VLCFA studies suggestive of X-linked ALD
	Definite	Carrier Female	Elevated^	Normal	Variant of uncertain significance *ABCD1* gene		
	Possible	Carrier Female	Normal	Normal	Variant of uncertain significance *ABCD1* gene		

^ In the pathogenic range

In Males and Females:

Zellweger Spectrum Disorder	Category	Plasma VLCFA	Plasmalogen	Clinical symptoms	Mutation analysis	Fibroblast studies
	Definite	Elevated^	Low	Present*	Two pathogenic variants in the same PEX gene	Untested or unknown
	Definite	Elevated^	Low	Present*	Untested or unknown	Consistent with ZSD
	Definite	Elevated^	Low	Not present	Two pathogenic variants in the same PEX gene	Untested or unknown
	Definite	Elevated^	Low	Not present	Untested or Unknown	Consistent with ZSD
	Definite	Elevated^	Low	Present*	Untested or Unknown	Untested or unknown
	Possible	Elevated^	Low	Not present	Untested or Unknown	Untested or unknown
	Possible	Elevated^	Normal	Not present	Untested or Unknown	Untested or unknown

^ In the pathogenic range

* Clinical symptoms may include: Hypotonia in newborn period, failure to thrive, craniofacial abnormalities, abnormal liver function tests.

In Males and Females:

Peroxisomal Disorder -	Category	Plasma VLCFA	Clinical Symptoms	Plasmalogen	Mutation analysis	Family History
	PROBABLE	Elevated^	Not present	Normal	No mutation on sequencing, deletion/duplication not found	

^ In the pathogenic range

In Males and Females:

Acyl-CoA Oxidase Deficiency	Category	Plasma VLCFA	Plasmalogen	Mutation analysis	Fibroblast studies	Clinical Symptoms
	Definite	Elevated^	Normal	Two pathogenic mutations in the ACOX1 gene	Untested or unknown	Not present at birth
	Possible	Elevated^	Normal	Untested or unknown	Consistent with Acyl-CoA Oxidase Deficiency	Not present at birth

^ In the pathogenic range

In Males and Females:

	Category	Plasma VLCFA	Plasmalogen	Mutation analysis	Fibroblast studies	Clinical Symptoms
D-Bifunctional Protein Deficiency	Definite	Elevated^	Normal	Two pathogenic mutations in the HSD17B4 gene	Untested or unknown	Present*
	Possible	Elevated^	Normal	Untested or unknown	Consistent with D-Bifunctional Protein	Present*

^ In the pathogenic range

* Clinical symptoms may include: Hypotonia in newborn period, failure to thrive, craniofacial abnormalities, abnormal liver function tests.

In Males and Females:

	Category	Plasma VLCFA	Plasmalogen	Mutation analysis	Fibroblast studies	Clinical Symptoms
ABDC5	Definite	Elevated^	Normal	Two disease causing mutations	Untested or unknown	Not present at birth
	Definite	Elevated^	Normal	Untested or unknown	Consistent with ABCD5	Not present at birth

^ In the pathogenic range

In Males and Females:

	Category	Plasma VLCFA	Plasmalogen	Mutation analysis	Fibroblast studies	Clinical Symptoms
Non-peroxisomal Disorder	Definite	Normal	Normal	Mutation in one of the 7 known genes for Aicardi-Goutiéres Syndrome	Untested or unknown	Present**

** Clinical symptoms may include: Hypotonia in newborn period, failure to thrive, on CT scan, intracranial calcifications.

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SMA Newborn Screening

Case Definitions Tables

November 2019

Definitions created by a panel of experts is supported by the Health Resources and Services Administration (HRSA) under Cooperative Agreement # UG9MC30369 New Disorders Implementation Project.

Classification	Newborn Screen Molecular*		Post-Newborn Screen Molecular		Parental Molecular Testing Family History/Parental Genetic Testing	Clinical Symptoms at the time of Presentation**
	SMN1 Copy Number	SMN2 Copy Number	SMN1 Copy Number	SMN2 Copy Number		
Definite	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^	Any	Zero copies of SMN1 (presumed homozygous deletion) ^	Any		
Definite	2 pathogenic variants	Any	2 pathogenic variants	Any	Phasing is complete and confirms that variants are in trans or both parents are known to be carriers of the pathogenic variants identified	
Definite	2 pathogenic variants observed on two independently collected NBS specimens	Any	Unknown/ Not Done	Any	Phasing is complete and confirms that variants are in trans or both parents are known to be carriers of the	

					pathogenic variants identified	
Definite	Unknown/ Not Done/Screen Negative	Any	2 pathogenic variants observed on 2 independently collected specimens	Any	Phasing is complete and confirms that variants are in trans or both parents are known to be carriers of the pathogenic variants identified	
Definite	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^		Unknown/ Not Done	Unknown/ Not Done	Both parents are known carriers of SMN1 deletion	
Definite	Unknown/ Not Done /Screen Negative	Any	Zero copies of SMN1 (presumed homozygous deletion/conversion)	Any	Both parents are known carriers of SMN1 deletion	
Definite	Unknown/ Not Done /Screen Negative	Any	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^ Observed on two independently collected specimens	Any		
Definite	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^ observed on two independently collected NBS specimens	Any	Unknown/ Not Done			

Definite	Unknown/ Not Done /Screen Negative	Any	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^	Any		Clinical Symptoms present (see list)
Probable	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^	Any	Unknown/ Not Done	Any		Clinical Symptoms Present (see list)
Probable	2 pathogenic variants	Any	2 pathogenic variants		Phasing not done or not known	Clinical symptoms present (see list)
Probable	2 pathogenic variants observed on two independently collected NBS specimens	Any	Unknown/ Not Done		Phasing not done or not known	Clinical symptoms present (see list)
Probable	Unknown/ Not Done/Screen Negative	Any	2 pathogenic variants observed on 2 independent collected specimens		Phasing not done or not known	Clinical symptoms present (see list)
Possible	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^	Any	Unknown/ Not Done		Unknown/ Not Done	Unknown/ Not Done
Possible	Unknown/ Not Done /Screen Negative	Any	Zero copies of SMN1 (presumed homozygous deletion/conversion) ^	Any	Unknown/ Not Done	Unknown
Possible	2 pathogenic variants observed on two independently collected NBS specimens	Any	Unknown/ Not Done			

Possible	Unknown/ Not Done/Screen Negative	Any	2 pathogenic variants observed on 2 independently collected specimens			
Possible	2 pathogenic variants	Any	2 pathogenic variants			
Possible	2 pathogenic variants	Any	Unknown/ Not Done		Phasing not done or not known	Clinical symptoms present (see list)
Possible	Unknown/ Not Done	Any	2 pathogenic variants		Phasing not done or not known	Clinical symptoms present (see list)
Possible	1 pathogenic variant and 1 variant of unknown significance	Any	1 pathogenic variant and 1 variant of unknown significance			
Possible	1 pathogenic variant and 1 variant of unknown significance	Any	1 pathogenic variant and 1 variant of unknown significance			Clinical symptoms present (see list)
Possible	1 pathogenic variant and 1 variant of unknown significance	Any	1 pathogenic variant and 1 variant of unknown significance		Phasing is complete and confirms that variants are in trans or both parents are known to be carriers of the variants identified	With or without clinical symptoms
Possible	2 variants of unknown significance	Any	2 variants of unknown significance			
Possible	2 variants of unknown significance	Any	2 variants of unknown significance		Phasing is complete and confirms that variants are in trans or both parents are known to be carriers of the variants identified	With or without clinical symptoms
Possible	Unknown/ Not Done /Screen Negative	Any	2 variants of unknown significance			Clinical symptoms present (see list)

KEY:

^ Presumed homozygous deletion/conversion: true deletion of exon 7 (or larger) or for which there has been a gene conversion of exon 7 (or more)

* Programs need to ensure specimens are valid, taking into account NICU status and inhibitor use

** Clinical symptoms include electromyography evidence of motor neuron disease, absent reflexes, fasciculations, feeding difficulty, hypotonia, respiratory difficulty, weakness