Informative Markers for Supplemental Newborn Screening at Mayo Clinic

(Amino Acids and Acylcarnitine Species Identified, Differential Diagnoses, and Required Follow-Up Testing)

Informative marker	Differential diagnosis			Second-tier test	Initial confirmatory testing[B]	Mayo Clinic Test Codes
	Primary conditions[A]	Secondary conditions[A]	Other conditions			
Alanine (Ala)	-	-	LA	-	PAA, L&P	AAQP LAA PYR
Arginine (Arg)	ARG	CIT II	-	-	PAA	AAQP
Argininosuccinic acid (ASA)	ASL	-	-	-	PAA, UOA	AAQP OAU
Citrulline (Cit)	CIT I, ASL	CIT II	PC, OTC, CPS	-	PAA, UOA	AAQP OAU
Glutamic acid (Glu)	-	-	OTC, CPS	-	PAA, UOA	AAQP OAU
Glutamine+Pyroglutamic acid (Gln+Pyrog)	-	-	OXO-PRO, OTC, CPS	-	PAA, UOA, OROT	AAQP OAU OROT
Glycine (Gly)	-	-	NKHG	-	PAA, CSF-Gly	AAQP AACSF
Leucine/Isoleucine/ OH Proline (Xle)	MSUD	-	PDH (E3), OH-PRO	Allo-Ile	PAA, UOA	AAQP OAU
Lysine (Lys)	-	DE-RED	H-LYS	-	PAA, PAC	AAQP ACRN
Methionine (Met)	CBS	MET	MTHFR, Cbl E, Cbl G, Cbl D v1	tHcy	PAA, tHcy	AAQP HCYSP
Ornithine+Asparagine (Orn+Asn)	-	-	H-ORN, HHH	-	PAA, UAA	AAQP AAPD
Phenylalanine (Phe)	PKU	H-PHE, BIOPT (BS), BIOPT (REG)	untreated maternal PKU[C]	-	PAA, UPTR	AAQP NA
Proline (Pro)	-	-	HPI, HPII, LA	-	PAA	AAQP
Succinylacetone (SUAC)	TYR I	-	-	-	PAA, UOA, AFP	AAQP OAU AFP
Threonine (Thr)	-	CIT II	-	-	PAA	AAQP
Tyrosine (Tyr)	TYR I	TYR II, TYR III	-		PAA, UOA	AAQP OAU
Valine (Val)	MSUD	-	PDH (E3), VAL	Allo-Ile	PAA, UOA	AAQP OAU
Carnitine (C0)	CUD	CPT I	untreated maternal cases (CUD, GA I, 3MCC)[C]	-	PCarn, PAC	CARN ACRN
Propionylcarnitine (C3)	PA, MCD, MUT, CBL A/B	CBL C/D	SUCLA2, untreated maternal Vit B12 def[C]	MMA, MCA, tHcy	PCarn, PAC, UOA	CARN ACRN OAU
Formiminoglutamic acid (FIGLU)	-	SCAD, IBG	FIGLU-aciduria	-	PAC, UOA	ACRN OAU
Butyryl-/Isobutyrylcarnitine (C4)	-	SCAD, IBG, GA II	EE, FIGLU-aciduria	EMA	UAG, UOA, PAC, UAC	ACYLG OAU ACRN C4U -or- C5DCU -or- C5OHU
Tiglylcarnitine (C5:1)	BKT	2M3HBA	-	-	UOA, PAC, UAC	OAU ACRN C4U -or- C5DCU -or- C5OHU

Isovaleryl-/2-Methylbutyrylcarnitine (C5)	IVA	2MBG, GA II	EE	-	UAG, UOA, PAC	ACYLG OAU ACRN
OH Butyrylcarnitine (C4-OH)	BKT	2M3HBA, S/MCHAD	-	-	PAC, UOA	ACRN OAU
Hexanoylcarnitine (C6)	MCAD	GA II	-	-	UAG, UOA, PAC	ACYLG OAU ACRN
OH Isovalerylcarnitine (C5-OH)	3MCC, HMG, BKT, MCD	2M3HBA, 3MGA	BIOT (partial)	-	UOA, PAC, UAC	OAU ACRN C4U -or- C5DCU -or- C5OHU
Octanoylcarnitine (C8)	MCAD	GA II, MCKAT	-	-	UAG, UOA, PAC	ACYLG OAU ACRN
Malonyl-/OH Octanoylcarnitine (C3DC)	-	MAL, MCKAT	-	-	UOA, PAC	OAU ACRN
Decadienoylcarnitine (C10:2)	-	DE-RED	-	-	PAA, OAC	AAQP ACRN
Decenoylcarnitine (C10:1)	MCAD	GA II	-	-	UAG, UOA, PAC	ACYLG OAU ACRN
Decanoylcarnitine (C10)	MCAD	GA II	-	-	UAG, UOA, PAC	ACYLG OAU ACRN
Succinyl-/Methylmalonylcarnitine (C4DC)	MUT, Cbl A,B	-	SUCLA2	MMA, MCA, tHcy	UOA, PAC	OAU ACRN
Glutaryl-/OH Decanoylcarnitine (C5DC)	GA I	GA II	-	-	UOA, PAC, UAC	OAU ACRN C4U -or- C5DCU -or- C5OHU
Dodecenoylcarnitine (C12:1)	VLCAD	-	-	-	UOA, PAC, DNA	OAU ACRN VLCMS
Dodecanoylcarnitine (C12)	VLCAD	-	-	-	UOA, PAC, DNA	OAU ACRN VLCMS
Methylglutarylcarnitine (C6DC)	HMG	-	-	-	UOA, PAC, UAC	OAU ACRN C4U -or- C5DCU -or- C5OHU
Tetradecanedioylcarnitine (C14:2)	VLCAD, LCHAD/TFP	GA II	-	-	UOA, PAC, DNA	OAU ACRN VLCMS
Tetradecenoylcarnitine (C14:1)	VLCAD, LCHAD/TFP	GA II	-	-	UOA, PAC, DNA	OAU ACRN VLCMS
Tetradecanoylcarnitine (C14)	VLCAD, LCHAD/TFP	CACT, CPT II	-	-	UOA, PAC, DNA	OAU ACRN VLCMS
Palmitoylcarnitine (C16)	VLCAD	CPT I (low), CACT, CPT II	-	-	PCarn, PAC, UOA	CARN ACRN OAU
OH Hexadecenoylcarnitine (C16:1-OH)	LCHAD/TFP	-	-	-	PCarn, PAC, UOA	CARN ACRN OAU
OH Palmitoylcarnitine (C16-OH)	LCHAD/TFP	-	-	-	PCarn, PAC, UOA	CARN ACRN OAU

Linoleylcarnitine (C18:2)	LCHAD/TFP	CPT II	-	-	PCarn, PAC, UOA	CARN ACRN OAU
Oleylcarnitine (C18:1)	VLCAD, LCHAD/TFP	CPT I (low), CACT, CPT II, GA II	-	-	PCarn, PAC, UOA	CARN ACRN OAU
Stearylcarnitine (C18)	VLCAD	CPT I (low), CACT, CPT II, GA II	-	-	PCarn, PAC, UOA	CARN ACRN OAU
OH Oleylcarnitine (C18:1-OH)	LCHAD/TFP	-	-	-	PCarn, PAC, UOA	CARN ACRN OAU
OH Stearylcarnitine (C18-OH)	LCHAD/TFP	-	-	-	PCarn, PAC, UOA	CARN ACRN OAU

[A]Primary and secondary conditions based on current recommendations by the US Secretary of Health and Human Services
[B]Tests performed in other than dried blood spot samples; may include additional tests when newborn is clinically symptomatic. More information on follow-up requirements can be found at: http://www.ncbi.nlm.nih.gov/books/NBK55832/
[C]Detection is possible because of secondary carnitine deficiency of the newborn

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Abreviations:
AC, sum of selected species (C0+C2+C3+C16+C18+C18:1); AFP, alpha fetoprotein; Allo-Ile, allo-isoleucine; ARG, arginase deficiency; ASL, argininosuccinate lyase deficiency; BIOPT (BS), GTP cyclohydrolase and 6-Pyruvoil tetrahydropterin synthase deficiencies; BIOPT (REG), Dihydropteridine reductase and Pterin-4α-carbinolamine dehy-dratase 2 deficiencies; BIOT, biotinidase deficiency; BKT, beta-ketothiolase deficiency; CACT, carnitine-acylcarnitine translocase deficiency; Cbl, cobalamin metabolism defect, complementation type A/B/C/D variant 1/E or F; CBS, cys-tathionine beta-synthase deficiency; CIT II, citrullinemia type II (citrin deficiency); CPS, carbamoyl phophaste syn-thetase type I deficiency; CPT I, carnitine palmitoyltransferase type I deficiency; CPT II, carnitine palmitoyltransferase type II deficiency; CSF-Gly, glycine in cerebrospinal fluid; CUD, carnitine uptake defect; DE-RED, 2,4-Dienoyl-CoA reductase deficiency; DNA, molecular genetic analysis; EE, ethylmalonic encephalopathy; EMA, ethylmalonic acid; GA I, glutaric aciduria type I; GA II, glutaric aciuria type II; Gal-1-P, galactose-1-phosphate in red blood cells; GALE, UDP-galactose-4-epimerase deficiency; GALK, galactokinase deficiency; GALT, galactose-1-phospate uridyltransferase deficiency; G6PD, glucose-6-phosphate dehydrogenase deficiency; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria syndrome; H-LYS, alpha-aminoadipic semialdehyde synthase deficiency; HMG, 3-hydroxy methyl-glutaryl-CoA synthase deficiency; H-PHE, mild phenylalanine hydroxylase deficiency; HPI, hyperprolinemia type I (proline oxidase deficiency); HPII, hyperprolinemia type II (pyrroline-5-carboxylate dehydrogenase deficiency); IBG, isobutyryl-CoA dehydrogenase deficiency; IVA, isovaleric acidemia; LA, lactic acidemia (primary or secondary); LCHAD/TFP, long-chain 3-hydroxy acyl-CoA dehydrogenase deficiency, trifunctional protein deficiency; L&P, plasma lactate and pyruvate; MAL, malo-nyl-CoA decarboxylase deficiency; 2MBG, 2-methylbutyrylglycinuria; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; 3MCC, 3-methylcrotonyl-CoA carboxylase deficiency; MCD, multiple carboxylase deficiency; MCKAT, medium-chain 3-ketoacyl-CoA thiolase deficiency; MET, Methionine adenosyltransferase I/III, S-adenosylhomocysteine hydrolase, and Glycine N-methyltransferase deficiencies; 3MGA, 3-methylglutaconic aciduria type I; 2M3HBA, 2-methyl 3-hydroxybutyric aciduria; MSUD, maple syrup urine disease; MTHFR, methylene tetrahy-drofolate reductase deficiency; MUT, methylmalonyl-CoA mutase deficiency; NKHG, non-ketotic hyperglycinemia; OAT, ornithine aminotransferase deficiency; OH-PRO, hydroxyprolinemia (hydroxy-L-proline oxidase deficiency); OROT, urine orotic acid; OTC, ornithine transcarbamylase deficiency; OXO-PRO, 5-oxoprolinemia (glutathione synthetase deficiency); PAA, plasma amino acids; PAC, plasma acylcar-nitines; PC, pyruvate carboxylase deficiency; PCarn, plasma carnitine; PDH (E3), pyruvate dehydrogenase component E3 deficiency (dihydrolipoamide dehydrogenase deficiency); PKU, phenylalanine hydroxylase deficiency; RBC, red blood cells; SCAD, short-chain acyl-CoA dehydrogenase deficiency; S/MCHAD, short-/medium-chain acyl-CoA dehydrogenase deficiency; SUCLA2, succinyl-CoA synthase deficiency; tHcy, total homocysteine; TYR I, tyrosinemia type I (fumarylacetoacetase deficiency); TYR II, tyrosinemia type II (tyrosine aminotransferase deficiency); TYR III, tyrosinemia type III (4-hydroxyphenylpyruvate dioxygenase deficiency); UAA, urine amino acids; UAC, urine acylcarnitines; UAG, urine acylglycines; UOA, urine organic acids; UPTR, urine pteridines; VAL, valine transaminase deficiency; VLCAD, very long-chain acyl-CoA dehydrogenase deficiency; WBC, white blood cells.