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Inborn Errors of Metabolism That Cause Sudden Infant Death

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1 **Inborn errors of metabolism causing Sudden Infant Death: a systematic review with**
2 **implications for population neonatal screening programs**

3
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26 **Abbreviations:** DBS, dried blood spot; IEMs, inborn errors of metabolism; MeSH, Medical
27 Subject Headings; NBS, neonatal bloodspot screening; RS, Reye syndrome; SID, sudden
28 infant death; TMS, tandem mass spectrometry.

29

30 **Key words:** neonatal screening; inborn error of metabolism; mitochondrial fatty acid
31 oxidation; Reye syndrome; sudden infant death; tandem mass spectrometry; treatment;
32 metabolic autopsy.

33

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35

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37

38 **Conflict of interest:** The authors have no conflicts of interest to disclose.

39

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42 search strategy.

43 **Abstract:**

44 *Background:* Many inborn errors of metabolism (IEM) may present as sudden infant death
45 (SID). Nowadays increasing numbers of patients with an IEM are identified
46 presymptomatically by population neonatal screening (NBS) programs. However, some
47 patients escape early detection because their symptoms and signs start before NBS test results
48 become available, die even before the sample for NBS has been drawn, or due to IEMs which
49 are not included in the NBS programs.

50 *Objectives & methods:* A comprehensive systematic literature review to identify all IEMs
51 associated with SID, including their treatability and detectability by NBS technologies. Reye
52 syndrome (RS) was included in the search strategy because this condition can be considered
53 as a possible pre-stage of SID in a continuum of aggravating symptoms.

54 *Results:* 43 IEMs were identified that were associated with SID and/or RS. Of these IEMs (a)
55 26 can already present during the neonatal period, (b) treatment is available for at least 32,
56 and (c) 26 can currently be identified by analysis of acylcarnitines and amino acids in dried
57 bloodspots.

58 *Conclusion:* We advocate extensive analysis of amino acids and acylcarnitines in
59 blood/plasma/dried bloodspots and urine for all children who died suddenly and/or
60 unexpectedly, including neonates in whom a blood spot for the routine NBS program has not
61 yet been drawn. The application of combined metabolite screening and DNA sequencing
62 techniques would facilitate fast identification and maximal diagnostic yield. This is important
63 information for both clinicians who need to maintain clinical awareness, and for decision-
64 makers to improve population NBS programs.

65

66 **Introduction:**

67 Many inborn errors of metabolism (IEM) that cause cellular energy deficiency and/or
68 intoxication are associated with sudden infant death (SID). Based on retrospective studies,
69 approximately 0.9-6% of all SID cases represent IEMs.[1-3] Although these studies were
70 subject to several forms of selection bias, they form the rationale behind metabolic autopsy
71 protocols for young children, which include analyses of amino acid and acylcarnitine profiles
72 in plasma/urine.[4]

73 Since the 1990s, tandem mass spectrometry (TMS) in dried blood spots (DBS) has
74 been developed to perform high-throughput simultaneous quantitative analysis of different
75 diagnostic metabolites in small amounts in biological samples.[5] As a consequence, in the
76 last two decades population neonatal bloodspot screening (NBS) programs have been
77 expanded with many IEMs. Patients with treatable IEMs can remain undetected by population
78 NBS programs for several reasons. In some IEMs, symptoms and signs including death
79 already occur prior to the NBS test results becoming available or even before the blood spot
80 has been drawn, annulling the benefits of NBS.[6-10] This is especially relevant in areas
81 where neonatal blood is collected relatively late, for instance in the Netherlands (i.e. 72-168
82 hours after birth).[11, 12] Between different areas worldwide, population NBS programs
83 differ with respect to methodological aspects and disorders to screen for.

84 Systematic studies on the percentage of IEMs among SID cases are required as,
85 although rare, preventable SID cases due to treatable IEMs still occur. Therefore, we
86 performed this comprehensive systematic literature review to identify IEMs (1) that are
87 associated with SID, (2) have clinical ascertainment during the neonatal period, (3) are
88 treatable and (4) are detectable by TMS.

89

90 **Methods:**

91 *Search strategy*

92 A literature search for relevant references was performed according to the Cochrane
93 Collaboration methodology. CINAHL, Cochrane, Pubmed and Embase public databases were
94 searched using both Medical Subject Headings (MeSH) terms and free text. A detailed
95 presentation and assessment of the search strategy, including the Preferred Reporting Items
96 for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist, is presented
97 in Supplemental Data 1. Figure 1 presents the flowchart of the detailed search strategy
98 together with the steps of the systematic review.

99 The following search terms were included to further optimize our search strategy. The
100 term “mitochondrial fatty acid oxidation” was included because, based on previous studies
101 and our personal expertise, this disease group has the highest incidence among IEMs
102 associated with both SID [1-3] and NBS programs.[6, 7, 10] SID is historically defined to
103 occur in the first year of life. We therefore expanded our search strategy with “sudden
104 unexpected death of infant”. Originally, Reye syndrome (RS) has been described as a non-
105 inflammatory encephalopathy in childhood, associated with hepatic dysfunction.[13] Since
106 the 1980s it has been recognized as a presenting symptom of IEMs rather than being an
107 etiologic diagnosis.[14] We considered RS as a potential pre-stage of SID in a continuum of
108 aggravating symptoms. Therefore we also included the term “Reye syndrome” in our search
109 strategy.

110 All reports published since 1990 were included, corresponding with the first
111 publications about the availability of TMS and general progressions made in the field of
112 molecular and enzymatic confirmatory testing in the field of IEMs. References published
113 before 1990 were only included when available upon request. Two independent reviewers
114 (GK and TD) performed title and abstract screenings. Consensus on inclusion was reached

115 during regular meetings. Subsequently, three independent (WvR, GK and TD) screened the
116 full text articles of all selected references. The inclusion of a diagnosis as a cause of SID
117 and/or RS was based on the presence of detailed patient data and a confirmed diagnosis in the
118 full text articles. Specific exclusion criteria were (1) no detailed patient data reported; (2) lack
119 of accessibility of the articles; (3) confirmatory metabolite, molecular or enzymatic studies
120 were inconclusive; (4) when there had been a (possible) additionally contributing cause of
121 death; (5) patients suffering from SID and/or RS aged above 18 years and/or (6) abstract
122 and/or article not available in English or Dutch language.

123

124 *Data analysis*

125 All IEMs were classified according to the Society for the Study of Inborn Errors of
126 Metabolism classification of IEMs.[15] Based on the included references, associations
127 between confirmed diagnoses and SID and/or RS were documented. For example, a plus sign
128 in the SID column in Table 1 indicates that the particular IEM has been associated with SID
129 in at least one of the corresponding references presented in Supplemental Table 1. Neonatal
130 clinical presentation was reported based on detailed patient data of the included references.
131 Based on recent textbooks and literature, treatability [16] and detectability by TMS in a DBS
132 [17-19] were documented, respectively.

133

134 **Results:**

135 This systematic review included a total of 136 references. Table 1 presents the 43 IEMs
136 associated with either SID and/or RS, concerning mostly disorders of mitochondrial fatty acid
137 oxidation, the urea cycle and organic acidurias. References of all included articles are
138 presented in Supplemental Table 1. Out of these 43 IEMs, minimally 26 already presented
139 during the neonatal period of which 15 are both treatable and detectable by TMS
140 methodologies. In at least 32 out of the 43 IEMs, a specific dietary and/or pharmacological
141 treatment is available in order to prevent clinical presentation. Identification by population
142 NBS programs by TMS analysis of amino acids and/or acylcarnitines in DBS is possible in 26
143 out of the 43 IEMs.

144

145 **Discussion:**

146 This unique systematic literature review identified at least 43 IEMs that are associated with
147 SID and/or RS, of which 26 can already present during the neonatal period. At least 32 out of
148 43 are considered as treatable disorders and 26 out of 43 are currently detectable by TMS
149 analysis of amino acids and/or acylcarnitines in DBS. The remaining 17 IEMs will not be
150 detected by current *metabolite* screening methods, but require additional testing either by
151 expanding the metabolic testing options or by *genetic* and/or *enzymatic* laboratory methods.
152 Out of the 26 IEMs in which clinical ascertainment within the neonatal period has been
153 reported, at least 15 are both treatable and detectable by TMS analysis. This is important
154 information to improve population NBS programs as early detection and subsequent treatment
155 may prevent clinical presentation and even death (Table 1). Moreover, with the results of our
156 study, diagnostic (laboratory) protocols can be improved for children (including neonates)
157 presenting with sudden/unexpected death.

158 There is no doubt that expanded population NBS programs have significantly
159 improved the outcomes of many patients, but there remains a subset of patients that
160 unfortunately escapes early identification.[20] First, one group escapes early identification
161 because limited numbers of IEMs are included in the NBS programs. It is important to realize
162 that population NBS programs differ worldwide, and may even differ within countries.
163 Second, another group escapes early identification because symptoms and signs present
164 before NBS test results become available or even before the blood spot has been drawn. This
165 is aggravated by relative late NBS blood obtainment and/or follow-up after positive test
166 results in some areas/countries. In the Netherlands neonatal blood for the NBS test is collected
167 between 72-168 hours after birth.[11, 12] In 2013, the response rate for the NBS program was
168 99.35%. Referral to a metabolic physician was initiated before day 8 in 62% of the positive
169 neonates, whereas 441 out of 173,118 newborns died (etiology not specified) before the NBS

170 blood spot could be drawn.[11] Reports from population NBS programs from Australia, the
171 USA and Germany present patients with clinical ascertainment and sometimes even neonatal
172 death before NBS test results have become available (indicated with ** in table 1).[6, 7, 10]
173 In line with these reports, in our country since the expansion of the NBS program (Table 1),
174 clinical symptoms and signs preceded the NBS test results, sometimes even leading to early
175 death, in cases of very long-chain acyl-CoA dehydrogenase deficiency, long-chain 3-
176 hydroxyacyl-CoA dehydrogenase deficiency/mitochondrial trifunctional protein deficiency,
177 medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease and
178 galactosemia (data unpublished). Last, patients may escape early identification due to false-
179 negative NBS results, (for example patients with carnitine transporter deficiency or very long-
180 chain acyl-CoA dehydrogenase deficiency [21, 22]) or (pre-)analytical reasons, which is of
181 concern for patients with carnitine palmitoyltransferase 2 deficiency [23]. These examples stir
182 the debate on whether the NBS test should be performed earlier in life and/or twice at two
183 different timings.

184 The general view on ‘the metabolic autopsy’ has originated from case studies and
185 small retrospective cohort studies that introduced bias.[4] It is generally recognized that low
186 incidences and aspecific symptoms and signs cause underdiagnosis of IEMs.[9] The current
187 study strengthens the rationale why – despite low incidences of the individual IEMs –
188 neonates who died deserve at least a TMS analysis of amino acids and acylcarnitines in a
189 DBS, when feasible. For most of the disorders listed in Table 1, the associated recurrence rate
190 for affected families is at least 25%.

191 Several methodological issues of this study should be mentioned. First, the
192 retrospective study designs of many included cohort studies and case studies could have
193 introduced both a publication bias and a data availability bias as 1) reports do not always
194 describe detailed patient data and 2) obviously not all SID cases due to IEMs have been

195 reported in literature. Second, there are many factors, including aspecific symptoms, causing
196 underdiagnosis of IEMs in neonates.[9] Third, despite our extensive and detailed search
197 strategy, we cannot exclude that few references have been missed. The fact that after
198 including the full text articles in the first round (n=91) new references still emerged via the
199 reference lists of excluded and included full text articles emphasizes this once more. In order
200 to optimize the search strategy, we conducted the second (n=44) and third (n=1) screening
201 rounds. Fourth, in medical literature the definition of SID is not always applied consistently
202 with regard to age ranges and clinical symptoms and signs. In an attempt to overcome this
203 issue, we added the term “sudden unexpected death of infant” to our search strategy. Last,
204 some included IEMs exemplify one protein deficiency in a large metabolic pathway involving
205 many enzymes and transporters that potentially could cause a similar clinical picture.
206 Therefore, we believe, based on our systematic review, that the IEMs included in Table 1
207 should be considered as the minimal number of IEMs associated with SID and/or RS. Despite
208 expanding NBS programs, clinical awareness needs to remain high amongst neonatologists
209 and pediatricians as many IEMs have not been implemented in NBS programs. Early
210 recognition of clinical presentations and subsequent diagnostic testing can possibly prevent
211 fatal outcomes.[24]

212 In summary, our systematic review identified the IEMs that are associated with RS
213 and SID, a significant proportion of them being treatable disorders. Therefore in our opinion
214 analysis of amino acids and acylcarnitines in blood/plasma/DBS and urine should be part of
215 post-mortem diagnostic protocols, next to isolation of DNA and preferentially, material for
216 functional tests such as analysis of cultured skin fibroblasts. To date, the combination of
217 metabolite screening and DNA sequencing techniques would harbor the best of both methods,
218 i.e. fast identification and a high diagnostic yield.

219

220 **References:**

- 221 1 Boles RG, Buck EA, Blitzer MG, Platt MS, Cowan TM, Martin SK, Yoon H, Madsen JA,
222 Reyes-Mugica M, Rinaldo P: Retrospective biochemical screening of fatty acid oxidation
223 disorders in postmortem livers of 418 cases of sudden death in the first year of life. *J Pediatr*
224 1998;132:924-933.
- 225 2 Chace DH, DiPerna JC, Mitchell BL, Sgroi B, Hofman LF, Naylor EW: Electrospray
226 tandem mass spectrometry for analysis of acylcarnitines in dried postmortem blood specimens
227 collected at autopsy from infants with unexplained cause of death. *Clin Chem* 2001;47:1166-
228 1182.
- 229 3 Green A, Preece MA, Hardy D: More on the metabolic autopsy. *Clin Chem* 2002;48:964-
230 965.
- 231 4 Ernst LM, Sondheimer N, Deardorff MA, Bennett MJ, Pawel BR: The value of the
232 metabolic autopsy in the pediatric hospital setting. *J Pediatr* 2006;148:779-783.
- 233 5 Millington DS, Kodo N, Norwood DL, Roe CR: Tandem mass spectrometry: a new method
234 for acylcarnitine profiling with potential for neonatal screening for inborn errors of
235 metabolism. *J Inherit Metab Dis* 1990;13:321-324.
- 236 6 Wilcken B, Wiley V, Hammond J, Carpenter K: Screening newborns for inborn errors of
237 metabolism by tandem mass spectrometry. *N Engl J Med* 2003;348:2304-2312.
- 238 7 Frazier DM, Millington DS, McCandless SE, Koeberl DD, Weavil SD, Chaing SH,
239 Muenzer J: The tandem mass spectrometry newborn screening experience in North Carolina:
240 1997-2005. *J Inherit Metab Dis* 2006;29:76-85.
- 241 8 Yusuf K, Jirapradittha J, Amin HJ, Yu W, Hasan SU: Neonatal ventricular tachyarrhythmias
242 in medium chain acyl-CoA dehydrogenase deficiency. *Neonatology* 2010;98:260-264.
- 243 9 Derks TG: Sweet and sour aspects of medium-chain acyl CoA dehydrogenase deficiency.
244 Commentary on K. Yusuf et al.: Neonatal ventricular tachyarrhythmias in medium chain acyl-
245 CoA dehydrogenase deficiency (*Neonatology* 2010;98:260-264). *Neonatology* 2010;98:265-
246 267.
- 247 10 Lindner M, Gramer G, Haege G, Fang-Hoffmann J, Schwab KO, Tacke U, Trefz FK,
248 Mengel E, Wendel U, Leichsenring M, Burgard P, Hoffmann GF: Efficacy and outcome of
249 expanded newborn screening for metabolic diseases--report of 10 years from South-West
250 Germany. *Orphanet J Rare Dis* 2011;6:44-1172-6-44.
- 251 11 Rijpstra A, Schonbeck Y, Verkerk PH: Evaluatie van de neonatale hielprikscreening bij
252 kinderen geboren in 2013. June 2015;10742.
- 253 12 Rijksinstituut voor Volksgezondheid en Milieu - Centrum voor Bevolkingsonderzoek:
254 Draaiboek Neonatale Hielprikscreening. March 2015;11.0.
- 255 13 Reye RD, Morgan G, Baral J: Encephalopathy and Fatty Degeneration of the Viscera. a
256 Disease Entity in Childhood. *Lancet* 1963;2:749-752.

- 257 14 Orlowski JP: Whatever happened to Reye's syndrome? Did it ever really exist?. Crit Care
258 Med 1999;27:1582-1587.
- 259 15 Society for the Study of Inborn Errors of Metabolism: Classification of Inborn Errors of
260 Metabolism 2011.
- 261 16 Saudubray JM, van den Berghe G, Walter JH: Inborn Metabolic Diseases: Diagnosis and
262 Treatment, ed 5, revised. Heidelberg, Springer, 2011.
- 263 17 McHugh D, Cameron CA, Abdenur JE, Abdulrahman M, Adair O, Al Nuaimi SA, Ahlman
264 H, Allen JJ, Antonozzi I, Archer S, Au S, Auray-Blais C, Baker M, Bamforth F, Beckmann K,
265 Pino GB, Berberich SL, Binard R, Boemer F, Bonham J, Breen NN, Bryant SC, Caggana M,
266 Caldwell SG, Camilot M, Campbell C, Carducci C, Bryant SC, Caggana M, Caldwell SG,
267 Camilot M, Campbell C, Carducci C, Cariappa R, Carlisle C, Caruso U, Cassanello M,
268 Castilla AM, Ramos DE, Chakraborty P, Chandrasekar R, Ramos AC, Cheillan D, Chien YH,
269 Childs TA, Chrastina P, Sica YC, de Juan JA, Colandre ME, Espinoza VC, Corso G, Currier
270 R, Cyr D, Czuczy N, D'Apolito O, Davis T, de Sain-Van der Velden MG, Delgado Pecellin C,
271 Di Gangi IM, Di Stefano CM, Dotsikas Y, Downing M, Downs SM, Dy B, Dymerski M,
272 Rueda I, Elvers B, Eaton R, Eckerd BM, El Mougy F, Eroh S, Espada M, Evans C, Fawbush
273 S, Fijolek KF, Fisher L, Franzson L, Frazier DM, Garcia LR, Bermejo MS, Gavrilov D,
274 Gerace R, Giordano G, Irazabal YG, Greed LC, Grier R, Grycki E, Gu X, Gulamali-Majid F,
275 Hagar AF, Han L, Hannon WH, Haslip C, Hassan FA, He M, Hietala A, Himstedt L,
276 Hoffman GL, Hoffman W, Hoggatt P, Hopkins PV, Hougaard DM, Hughes K, Hunt PR, Hwu
277 WL, Hynes J, Ibarra-Gonzalez I, Ingham CA, Ivanova M, Jacox WB, John C, Johnson JP,
278 Jonsson JJ, Karg E, Kasper D, Klopper B, Katakouzinis D, Khneisser I, Knoll D, Kobayashi
279 H, Koneski R, Kozich V, Kouapei R, Kohlmuller D, Kremensky I, la Marca G, Lavochkin
280 M, Lee SY, Lehotay DC, Lemes A, Lepage J, Lesko B, Lewis B, Lim C, Linard S, Lindner
281 M, Lloyd-Puryear MA, Lorey F, Loukas YL, Luedtke J, Maffitt N, Magee JF, Manning A,
282 Manos S, Marie S, Hadachi SM, Marquardt G, Martin SJ, Matern D, Mayfield Gibson SK,
283 Mayne P, McCallister TD, McCann M, McClure J, McGill JJ, McKeever CD, McNeilly B,
284 Morrissey MA, Moutsatsou P, Mulcahy EA, Nikoloudis D, Norgaard-Pedersen B, Oglesbee
285 D, Oltarzewski M, Ombrone D, Ojodu J, Papakonstantinou V, Reoyo SP, Park HD, Pasquali
286 M, Pasquini E, Patel P, Pass KA, Peterson C, Pettersen RD, Pitt JJ, Poh S, Pollak A, Porter C,
287 Poston PA, Price RW, Queijo C, Quesada J, Randell E, Ranieri E, Raymond K, Reddic JE,
288 Reuben A, Ricciardi C, Rinaldo P, Rivera JD, Roberts A, Rocha H, Roche G, Greenberg CR,
289 Mellado JM, Juan-Fita MJ, Ruiz C, Ruoppolo M, Rutledge SL, Ryu E, Saban C, Sahai I,
290 Garcia-Blanco MI, Santiago-Borrero P, Schenone A, Schoos R, Schweitzer B, Scott P,
291 Seashore MR, Seeterlin MA, Sesser DE, Sevier DW, Shone SM, Sinclair G, Skrinska VA,
292 Stanley EL, Strovel ET, Jones AL, Sunny S, Takats Z, Tanyalcin T, Teofoli F, Thompson JR,
293 Tomashitis K, Domingos MT, Torres J, Torres R, Tortorelli S, Turi S, Turner K, Tzanakos N,
294 Valiente AG, Vallance H, Vela-Amieva M, Vilarinho L, von Dobein U, Vincent MF, Vorster
295 BC, Watson MS, Webster D, Weiss S, Wilcken B, Wiley V, Williams SK, Willis SA,
296 Wootner M, Wright K, Yahyaoui R, Yamaguchi S, Yssel M, Zakowicz WM: Clinical
297 validation of cutoff target ranges in newborn screening of metabolic disorders by tandem
298 mass spectrometry: a worldwide collaborative project. Genet Med 2011;13:230-254.
- 299 18 ACMG Work Group on Management of Pompe Disease, Kishnani PS, Steiner RD, Bali D,
300 Berger K, Byrne BJ, Case LE, Crowley JF, Downs S, Howell RR, Kravitz RM, Mackey J,
301 Marsden D, Martins AM, Millington DS, Nicolino M, O'Grady G, Patterson MC, Rapoport

- 302 DM, Slonim A, Spencer CT, Tifft CJ, Watson MS: Pompe disease diagnosis and management
303 guideline. *Genet Med* 2006;8:267-288.
- 304 19 Gonzalez EC, Marrero N, Frometa A, Herrera D, Castells E, Perez PL: Qualitative
305 colorimetric ultramicroassay for the detection of biotinidase deficiency in newborns. *Clin*
306 *Chim Acta* 2006;369:35-39.
- 307 20 Marsden D, Larson C, Levy HL: Newborn screening for metabolic disorders. *J Pediatr*
308 2006;148:577-584.
- 309 21 Lund AM, Hougaard DM, Simonsen H, Andresen BS, Christensen M, Duno M,
310 Skogstrand K, Olsen RK, Jensen UG, Cohen A, Larsen N, Saugmann-Jensen P, Gregersen N,
311 Brandt NJ, Christensen E, Skovby F, Norgaard-Pedersen B: Biochemical screening of
312 504,049 newborns in Denmark, the Faroe Islands and Greenland--experience and
313 development of a routine program for expanded newborn screening. *Mol Genet Metab*
314 2012;107:281-293.
- 315 22 Ficicioglu C, Coughlin CR, 2nd, Bennett MJ, Yudkoff M: Very long-chain acyl-CoA
316 dehydrogenase deficiency in a patient with normal newborn screening by tandem mass
317 spectrometry. *J Pediatr* 2010;156:492-494.
- 318 23 de Sain-van der Velden MG, Diekman EF, Jans JJ, van der Ham M, Prinsen BH, Visser G,
319 Verhoeven-Duif NM: Differences between acylcarnitine profiles in plasma and bloodspots.
320 *Mol Genet Metab* 2013;110:116-121.
- 321 24 Derks TG, Jakobs H, Gerding A, Niezen-Koning KE, Reijngoud DJ, Smit GP: Deficiency
322 of the fatty-acid oxidising enzyme medium-chain acyl-CoA dehydrogenase (MCAD) in an
323 adult, detected during a neonatal screening programme. *Ned Tijdschr Geneesk*
324 2004;148:2185-2190.
- 325 25 Health Council of the Netherlands: Neonatal screening: new recommendations
326 2015;2015/08.

327
328

329 **Legends to tables and figures:**

330 **Figure 1. Flowchart of detailed search strategy.**

331 Legend: CINAHL, Cochrane, Pubmed and Embase were searched using both MeSH terms
332 and free text ("Metabolism, Inborn Errors"[Mesh] OR "inborn errors of metabolism" OR
333 "mitochondrial fatty acid oxidation") AND ("Sudden Infant Death"[Mesh] OR "sudden infant
334 of death" OR "sudden infant death syndrome" OR "unexpected death" OR "sudden
335 unexpected death of infant" OR "Reye Syndrome"[Mesh]) AND (Humans[Mesh]) AND
336 ("Infant, Newborn, Child, Adolescent"[Mesh] OR newborn OR infant OR child). Search
337 strategy was conducted on February, 15th 2013. Due to the elapsed time between the
338 execution of the search strategy and the completion of the manuscript, the search strategy was
339 repeated on August, 28th 2015, to screen for possible extra IEMs. This lead to the inclusion of
340 only one additional IEM associated with either SIDS and/or RS: dihydrolipoamide
341 dehydrogenase deficiency (DLD deficiency; MIM #246900).

342

343 **Table 1. The IEMs associated with either SID and/or RS.**

344 Legend: *Dihydrolipoamide dehydrogenase deficiency (DLD deficiency; MIM #246900),
345 #Medium chain 3-ketoacyl-CoA thiolase deficiency (MCKAT deficiency; MIM #602199):
346 these IEMs were not included in the list of the Society for the Study of Inborn Errors of
347 Metabolism, but were found via the search strategy and therefore included as IEMs associated
348 with either SID and/or RS. †According to McHugh et al [17]; ‡according to Kishnani et al
349 [18]; §according to Gonzalez et al.[19] **Reported to have caused clinical ascertainment
350 and/or neonatal death before NBS test results were available.[6, 7, 10] ††Included in the
351 expanded Dutch population NBS program since 2007.[25] †††Recommended in 2015 for
352 expansion of the Dutch population NBS program.[25]