Supplementary file 1: Literature search log

MEDLINE search terms:

1) Leigh syndrome OR synonyms
    a. OR → Leigh-like syndrome OR synonyms
2) AND → Mitochondrial diseases OR synonyms
3) AND → Treatments + synonyms OR synonyms
4) NOT → Metabolic encephalopathies + synonyms
    a. OR → MELAS OR MERRF OR CPEO OR Kearns-Sayre syndrome OR Pearson syndrome
    b. OR → CFS/Fibromyalgia/ME
    c. OR → Cancer OR synonyms

Date	Database/Source	Language	Search Terms	No. results returned
10/09/2020	**MEDLINE (via PubMed)**	English	((((((((((((((((((("Leigh syndrome") OR ("Necrotizing encephalomyelopathy of Leigh")) OR ("Leigh's necrotizing encephalomyelopathy")) OR ("Subacute necrotizing encephalomyelopathy")) OR ("Subacute necrotising encephalomyelopathy")) OR ("Infantile subacute necrotizing encephalomyelopathy")) OR ("Juvenile subacute necrotizing encephalomyelopathy")) OR ("Adult-onset subacute necrotizing encephalomyelopathy")) OR ("X-linked subacute necrotizing encephalomyelopathy")) OR ("Classical leigh syndrome")) OR ("Leigh disease")) OR ("Leigh's disease")) OR (leigh disease[MeSH Terms])) OR (("OXPHOS deficienc*") OR ("Oxidative phosphorylation deficienc*"))) OR (("PDHc deficienc*") OR ("Pyruvate dehydrogenase deficienc*"))) OR (("Coenzyme Q10 deficienc*") OR ("CoQ10 deficienc*"))) OR ("Leigh-like syndrome*")) OR ((((((((((("Leigh-like syndrome*") OR ((("French-Canadian Leigh syndrome") OR (Saguenay-Lac-Saint-Jean)) OR ("LRPPRC"))) OR (("Alpers-Huttenlocher syndrome") OR (POLG))) OR ((("Valine catabolism defect") OR ("HIBCH deficiency")) OR ("ECHS1 deficiency"))) OR (("GRACILE syndrome") OR (BCS1L))) OR ((("MEGDEL syndrome") OR ("3-methylglutaconic acidaemia")) OR (SERAC1))) OR (("Maternally inherited Leigh syndrome") OR (MTATP6))) OR (("Biotinidase responsive basal ganglia disease")	1,056

			OR (SLC19A3))) OR (("Thiamine responsive PDH deficiency") OR (PDHA1))) OR (("Lipoyltransferase 1 deficiency") OR (LIPT1))) OR (("ACAD9 deficiency") OR (ACAD9)))) AND ((((((((((Treatment) OR (("Ketogenic diet") OR ("Valine restricted diet"))) OR ((((((((((((Thiamine) OR (Riboflavin)) OR (Niacin)) OR (Biotin)) OR (CoQ10)) OR ("Coenzyme Q10")) OR (Idebenone)) OR (EPI-743)) OR (L-carnitine)) OR (a-lipoic acid)) OR (alpha-lipoic acid)) OR ("creatine monohydrate")) OR ("vitamin C")) OR ("Vitamin E"))) OR (Supplement*)) OR (Pyruvate)) OR (Rapamycin)) OR (Bezafibrate)) OR ((((Bezafibrate) OR (AICAR)) OR (Resveratrol)) OR ("Nicotinamide riboside"))) OR ("Oocyte spindle transfer")) OR (("mitochondrial replacement") OR ("Mitochondrial donation"))) OR (Therapy))) NOT (((((((("Wernicke's encephalopathy") OR (wernicke encephalopathy[MeSH Terms])) OR (hepatic encephalopathy[MeSH Terms])) OR ("Uraemic encephalopathy")) OR ("Drug induced encephalopathy")) OR (((Beriberi) OR (Ariboflavinosis)) OR (Pellagra))) OR (((((((((MELAS) OR (melas syndrome[MeSH Terms])) OR (merrf syndrome[MeSH Terms])) OR (MERRF)) OR (NARP)) OR (CPEO)) OR ("Kearns-Sayre syndrome")) OR ("Pearson syndrome")) OR ("stroke-like episodes")))) AND ((((("mitochondrial diseases"[MeSH Terms]) OR ("mitochondria"[MeSH Terms])) OR (mitochondria*)) OR ("mitochondrial disease*"))) NOT ((("Chronic fatigue syndrome") OR (fibromyalgia)) OR ("Myalgic encephalitis"))) NOT (((Cancer) OR (Carcinoma)) OR ("carcinoma"[MeSH Terms]))	
			Leigh syndrome OR synonyms	1,694
			Leigh-like syndrome OR synonyms	2,755
			Mitochondrial diseases	354,057
			Treatment OR synonyms	11,722,758
			Wernicke's encephalopathy OR Hepatic encephalopathy OR Uraemic encephalopathy OR Drug-induced encephalopathy	12,438
			Beriberi OR Ariboflavinosis OR Pellagra	4,777
			MELAS OR MERRF OR NARP OR CPEO OR Kearns-Sayre syndrome OR Pearson syndrome	4,951
			CFS OR Fibromyalgia OR Myalgic encephalitis	17,927
			Cancer OR synonyms	4,235,052
25/09/2020	**NIH ClinicalTrials.gov**	English	"Leigh Syndrome"	12
25/09/2020	**EU Clinical Trials Register**	English	"Leigh Syndrome"	2
25/09/2020	**Cochrane CENTRAL register of controlled trials**	English	"Leigh syndrome"	0

Supplementary file 2: List of articles and clinical trials screened

Reference	Source	Outcome
Alfadhel, M. *et al.* (2013) 'Biotin-responsive basal ganglia disease should be renamed biotin-thiamine-responsive basal ganglia disease: A retrospective review of the clinical, radiological and molecular findings of 18 new cases', *Orphanet Journal of Rare Diseases*. Orphanet J Rare Dis, 8(1). doi: 10.1186/1750-1172-8-83.	Publication	Positive
Bachmann-Gagescu, R., Merritt, J. L. and Hahn, S. H. (2009) 'A cognitively normal PDH-deficient 18-year-old man carrying the R263G mutation in the PDHA1 gene', *Journal of Inherited Metabolic Disease*, 32(SUPPL. 1), pp. 123–126. doi: 10.1007/s10545-009-1101-4.	Publication	Positive
Balasubramaniam, S. *et al.* (2016) 'Leigh-Like Syndrome Due to Homoplasmic m.8993T>G Variant with Hypocitrullinemia and Unusual Biochemical Features Suggestive of Multiple Carboxylase Deficiency (MCD)', *JIMD Reports*, 33, pp. 99–107. doi: 10.1007/8904.	Publication	Positive
Banka, S. *et al.* (2014) 'Expanding the clinical and molecular spectrum of thiamine pyrophosphokinase deficiency: A treatable neurological disorder caused by TPK1 mutations', *Molecular Genetics and Metabolism*, 113(4), pp. 301–306. doi: 10.1016/j.ymgme.2014.09.010.	Publication	Negative
Barnerias, C. *et al.* (2010) 'Pyruvate dehydrogenase complex deficiency: Four neurological phenotypes with differing pathogenesis', *Developmental Medicine and Child Neurology*, 52(2). doi: 10.1111/j.1469-8749.2009.03541.x.	Publication	Mixed
Briones, P. *et al.* (1996) 'Leigh syndrome due to pyruvate dehydrogenase Ela deficiency (point mutation R263G) in a Spanish boy', *J. Inher. Metab. Dis. 19*, 19, pp. 795–796.	Publication	Negative
Buda, P. *et al.* (2013) '"Drop attacks" as first clinical symptoms in a child carrying MTTK m.8344A>G mutation', *Folia Neuropathologica*, 51(4), pp. 347–354. doi: 10.5114/fn.2013.39726.	Publication	Positive
Cameron, J. M. *et al.* (2004) 'Deficiency of pyruvate dehydrogenase caused by novel and known mutations in the E1α subunit', *American Journal of Medical Genetics*, 131 A(1), pp. 59–66. doi: 10.1002/ajmg.a.30287.	Publication	Positive
Cardenas, J. F. and Amato, R. S. (2010) 'Compound heterozygous polymerase gamma gene mutation in a patient with alpers disease', *Seminars in Pediatric Neurology*. Elsevier Inc., 17(1), pp. 62–64. doi: 10.1016/j.spen.2010.02.012	Publication	Negative
Carrozzo, R. *et al.* (2014) 'Riboflavin responsive mitochondrial myopathy is a new phenotype of dihydrolipoamide dehydrogenase deficiency: The chaperon-like effect of vitamin B2', *Mitochondrion*. Elsevier, 18, pp. 49–57. doi: 10.1016/j.mito.2014.09.006.	Publication	Mixed
Castiglioni, C. *et al.* (2015) 'Pyruvate dehydrogenase deficiency presenting as isolated paroxysmal exercise induced dystonia successfully reversed with thiamine supplementation. Case report and mini-review', *European Journal of Paediatric Neurology*. Elsevier Ltd, 19(5), pp. 497–503. doi: 10.1016/j.ejpn.2015.04.008	Publication	Positive
Chen, Z. *et al.* (2015) 'Mild clinical manifestation and unusual recovery upon coenzyme Q10 treatment in the first Chinese Leigh syndrome pedigree with mutation m.10197 G>A', *Molecular Medicine Reports*. Spandidos Publications, 11(3), pp. 1956–1962. doi: 10.3892/mmr.2014.2911	Publication	Positive
Danis, D. *et al.* (2018) 'Mutations in SURF1 are important genetic causes of Leigh syndrome in Slovak patients', *Endocrine Regulations*, 52(2), pp. 110–118. doi: 10.2478/enr-2018-0013.	Publication	Negative
Debray, F. G. *et al.* (2008) 'Pyruvate dehydrogenase deficiency presenting as intermittent isolated acute ataxia', *Neuropediatrics*, 39(1), pp. 20–23. doi: 10.1055/s-2008-1077084	Publication	Negative

DeBrosse, S. D. *et al.* (2012) 'Spectrum of neurological and survival outcomes in pyruvate dehydrogenase complex (PDC) deficiency: Lack of correlation with genotype', *Molecular Genetics and Metabolism*. Elsevier Inc., 107(3), pp. 394–402. doi: 10.1016/j.ymgme.2012.09.001.	Publication	Mixed
Debs, R. *et al.* (2010) 'Biotin-responsive basal ganglia disease in ethnic Europeans with novel SLC19A3 mutations', *Arch Neurol.*, 67(1), pp. 126–30. doi: 10.1001/archneu-rol.2009.293	Publication	Positive
Dinwiddie, D. L. *et al.* (2013) Diagnosis of mitochondrial disorders by concomitant next- generation sequencing of the exome and mitochondrial genome', *Genomics*, 102(3), pp. 148–156. doi: 10.1016/j.ygeno.2013.04.013.Diagnosis.	Publication	Negative
Distelmaier, F. *et al.* (2013) 'Biotin-Responsive Basal Ganglia Disease: A Treatable Differential Diagnosis of Leigh Syndrome', *JIMD Reports*, 13, pp. 53–57. doi: 10.1007/8904.	Publication	Positive
Duncan, A. J. *et al.* (2009) 'A Nonsense Mutation in COQ9 Causes Autosomal-Recessive Neonatal-Onset Primary Coenzyme Q10 Deficiency: A Potentially Treatable Form of Mitochondrial Disease', *American Journal of Human Genetics*, 84(5), pp. 558–566. doi: 10.1016/j.ajhg.2009.03.018	Publication	Negative
El-Gharbawy, A. H. *et al.* (2011) 'Follow-up of a child with pyruvate dehydrogenase deficiency on a less restrictive ketogenic diet', *Molecular Genetics and Metabolism*. Elsevier Inc., 102(2), pp. 214–215. doi: 10.1016/j.ymgme.2010.11.001.	Publication	Positive
Enns, G. M. *et al.* (2012) 'Initial experience in the treatment of inherited mitochondrial disease with EPI-743', *Molecular Genetics and Metabolism*. Mol Genet Metab, 105(1), pp. 91–102. doi: 10.1016/j.ymgme.2011.10.009	Publication	Mixed
Eroglu, F. K. *et al.* (2018) 'Response to Early Coenzyme Q10 Supplementation Is not Sustained in CoQ10 Deficiency Caused by CoQ2 Mutation', *Pediatric Neurology*, 88, pp. 71–74. doi: 10.1016/j.pediatrneurol.2018.07.008.	Publication	Mixed
Fassone, E. *et al.* (2013) 'Treatable Leigh-like encephalopathy presenting in adolescence', *BMJ Case Reports*. BMJ Case Rep, 2013. doi: 10.1136/bcr-2013-200838.	Publication	Positive
Fraser, J. L. *et al.* (2014) 'Thiamine pyrophosphokinase deficiency causes a Leigh Disease like phenotype in a sibling pair: Identification through whole exome sequencing and management strategies', *Molecular Genetics and Metabolism Reports*. The Authors, 1(1), pp. 66–70. doi: 10.1016/j.ymgmr.2013.12.007.	Publication	Positive
Fujii, T. *et al.* (2002) 'Dichloroacetate therapy in Leigh syndrome with a mitochondrial T8993C mutation', *Pediatric Neurology*, 27(1), pp. 58–61. doi: 10.1016/S0887-8994(02)00378-8.	Publication	Positive
Fujii, T. *et al.* (2014) 'Efficacy of pyruvate therapy in patients with mitochondrial disease: A semi-quantitative clinical evaluation study', *Molecular Genetics and Metabolism*. Elsevier Inc., 112(2), pp. 133–138. doi: 10.1016/j.ymgme.2014.04.008.	Publication	Positive
Garone, C. *et al.* (2013) 'Mitochondrial Encephalomyopathy Due to a Novel Mutation in ACAD9', *JAMA Neurol. 2013*, 70(9), pp. 1177–1179.	Publication	Positive
Gerards, M. *et al.* (2013) 'Exome sequencing reveals a novel Moroccan founder mutation in SLC19A3 as a new cause of early-childhood fatal Leigh syndrome', *Brain*. Oxford University Press, 136(3), pp. 882–890. doi: 10.1093/brain/awt013.	Publication	Positive
Gerards, M. *et al.* (2011) 'Riboflavin-responsive oxidative phosphorylation complex i deficiency caused by defective ACAD9: New function for an old gene', *Brain*, 134(1), pp. 210–219. doi: 10.1093/brain/awq273	Publication	Positive
Ghezzi, D. *et al.* (2010) 'Severe X-Linked Mitochondrial Encephalomyopathy Associated with a Mutation in Apoptosis-Inducing Factor', *American Journal of Human Genetics*. The American Society of Human Genetics, 86(4), pp. 639–649. doi: 10.1016/j.ajhg.2010.03.002.	Publication	Mixed

Giribaldi, G. *et al.* (2012) 'Intermittent-relapsing pyruvate dehydrogenase complex deficiency: A case with clinical, biochemical, and neuroradiological reversibility', *Developmental Medicine and Child Neurology*, 54(5), pp. 472–476. doi: 10.1111/j.1469-8749.2011.04151.x	Publication	Positive
Grafakou, O. *et al.* (2003) 'Leigh syndrome due to compound heterozygosity of dihydrolipoamide dehydrogenase gene mutations. Description of the first E3 splice site mutation', *European Journal of Pediatrics*, 162(10), pp. 714–718. doi: 10.1007/s00431-003-1282-z.	Publication	Mixed
Haack, T. B. *et al.* (2015) 'Deficiency of ECHS1 causes mitochondrial encephalopathy with cardiac involvement', *Annals of Clinical and Translational Neurology*, pp. 492–509. doi: 10.1002/acn3.189.	Publication	Negative
Habarou, F. et al. (2017) 'Biallelic Mutations in LIPT2 Cause a Mitochondrial Lipoylation Defect Associated with Severe Neonatal Encephalopathy', American Journal of Human Genetics, 101(2), pp. 283–290. doi: 10.1016/j.ajhg.2017.07.001.	Publication	Mixed
Hasselmann, O. *et al.* (2010) 'Cerebral folate deficiency and CNS inflammatory markers in Alpers disease', *Molecular Genetics and Metabolism*. Elsevier Inc., 99(1), pp. 58–61. doi: 10.1016/j.ymgme.2009.08.005	Publication	Positive
Head, R. A. *et al.* (2005) 'Clinical and genetic spectrum of pyruvate dehydrogenase deficiency: Dihydrolipoamide acetyltransferase (E2) deficiency', *Annals of Neurology*, 58(2), pp. 234–241. doi: 10.1002/ana.20550	Publication	Positive
Huang, W. *et al.* (2019) 'Reduced thiamine binding is a novel mechanism for TPK deficiency disorder', *Molecular Genetics and Genomics*. Springer Berlin Heidelberg, 294(2), pp. 409–416. doi: 10.1007/s00438-018-1517-3	Publication	Positive
Huang, X. *et al.* (2017) 'Succinyl-CoA synthetase (SUCLA2) deficiency in two siblings with impaired activity of other mitochondrial oxidative enzymes in skeletal muscle without mitochondrial DNA depletion', *Molecular Genetics and Metabolism*, 120(3), pp. 213–222. doi: 10.1016/j.ymgme.2016.11.005	Publication	Negative
Illsinger, S. *et al.* (2020) 'Paroxysmal and non-paroxysmal dystonia in 3 patients with biallelic ECHS1 variants: Expanding the neurological spectrum and therapeutic approaches', *European Journal of Medical Genetics*, 63(11). doi: 10.1016/j.ejmg.2020.104046	Publication	Mixed
Invernizzi, F. *et al.* (2017) 'Thiamine-responsive disease due to mutation of tpk1: Importance of avoiding misdiagnosis', *Neurology*. Lippincott Williams and Wilkins, pp. 870–871. doi: 10.1212/WNL.0000000000004270.	Publication	Positive
João Silva, M. *et al.* (2009) 'Pyruvate dehydrogenase deficiency: Identification of a novel mutation in the PDHA1 gene which responds to amino acid supplementation', *European Journal of Pediatrics*, 168(1), pp. 17–22. doi: 10.1007/s00431-008-0700-	Publication	Positive
Joshi, C. N. *et al.* (2009) 'Ketogenic Diet in Alpers-Huttenlocher Syndrome', *Pediatric Neurology*. Elsevier Inc., 40(4), pp. 314–316. doi: 10.1016/j.pediatrneurol.2008.10.023.	Publication	Positive
Kara, B. *et al.* (2017) 'Pyruvate dehydrogenase-E1α deficiency presenting as recurrent acute proximal muscle weakness of upper and lower extremities in an 8-year-old boy', *Neuromuscular Disorders*, 27(1), pp. 94–97. doi: 10.1016/j.nmd.2016.11.001.	Publication	Positive
Karimzadeh, P. *et al.* (2019) '3-Hydroxyisobutyryl-CoA hydrolase deficiency in an Iranian child with novel HIBCH compound heterozygous mutations', *Clinical Case Reports*, 7(2), pp. 375–380. doi: 10.1002/ccr3.1998.	Publication	?
Kevelam, S. H. *et al.* (2013) 'Exome sequencing reveals mutated SLC19A3 in patients with an early-infantile, lethal encephalopathy', *Brain*, 136(5), pp. 1534–1543. doi: 10.1093/brain/awt054	Publication	Negative

Koga, Y. *et al.* (2012) 'Beneficial effect of pyruvate therapy on Leigh syndrome due to a novel mutation in PDH E1α gene', *Brain and Development*. The Japanese Society of Child Neurology, 34(2), pp. 87–91. doi: 10.1016/j.braindev.2011.03.003.	Publication	Mixed
Kohrogi, K. *et al.* (2015) 'Biotin-responsive basal ganglia disease: A case diagnosed by whole exome sequencing', *Journal of Human Genetics*. Nature Publishing Group, 60(7), pp. 381–385. doi: 10.1038/jhg.2015.35.	Publication	Positive
Kono, S. *et al.* (2009) 'Mutations in a Thiamine-Transporter Gene and Wernicke's-like Encephalopathy', *New England Journal of Medicine*. New England Journal of Medicine (NEJM/MMS), 360(17), pp. 1792–1794. doi: 10.1056/nejmc0809100.	Publication	Positive
Kouga, T. *et al.* (2018) 'Japanese Leigh syndrome case treated with EPI-743', *Brain and Development*. Elsevier B.V., 40(2), pp. 145–149. doi: 10.1016/j.braindev.2017.08.005.	Publication	Positive
Laugel, V. *et al.* (2007) 'Early-Onset Ophthalmoplegia in Leigh-Like Syndrome Due to NDUFV1 Mutations', *Pediatric Neurology*, 36(1), pp. 54–57. doi: 10.1016/j.pediatrneurol.2006.08.007.	Publication	Mixed
Lee, E. H. *et al.* (2006) 'A Korean female patient with thiamine-responsive pyruvate dehydrogenase complex deficiency due to a novel point mutation (Y161C) in the PDHA1 gene', *Journal of Korean Medical Science*, 21(5), pp. 800–804. doi: 10.3346/jkms.2006.21.5.800	Publication	Positive
Lee, J. S. *et al.* (2020) 'Genetic heterogeneity in Leigh syndrome: Highlighting treatable and novel genetic causes', *Clinical Genetics*, 97(4), pp. 586–594. doi: 10.1111/cge.13713.	Publication	Positive
Levy *et al.* (2014) 'Long Survival in Patients with Leigh Syndrome and the m. 10191T>C Mutation in MT-ND3: A Case Report and Review of the Literature', *J Child Neurol. 2014*, 29(1), pp. 105–110. doi: 10.1177/0883073813506783.Long.	Publication	Mixed
Li, D. *et al.* (2020) 'Eleven novel mutations and clinical characteristics in seven Chinese patients with thiamine metabolism dysfunction syndrome', *European Journal of Medical Genetics*. Elsevier Masson SAS, 63(10), p. 104003. doi: 10.1016/j.ejmg.2020.104003	Publication	Mixed
Liet, J.-M. *et al.* (2003) 'The effect of short-term dimethylglycine treatment on oxygen consumption in cytochrome oxidase deficiency: a double-blind randomized crossover clinical trial', *J Pediatr 2003;142:62-6)*, 142, pp. 62–6.	Publication	Negative
López, L. C. *et al.* (2006) 'Leigh syndrome with nephropathy and CoQ10 deficiency due to decaprenyl diphosphote synthase subunit 2 (PDSS2) mutations', *American Journal of Human Genetics*, 79(6), pp. 1125–1129. doi: 10.1086/510023.	Publication	Negative
Mahajan, A., Constantinou, J. and Sidiropoulos, C. (2017) 'ECHS1 deficiency-associated paroxysmal exercise-induced dyskinesias: case presentation and initial benefit of intervention', *Journal of Neurology*. Springer Berlin Heidelberg, 264(1), pp. 185–187. doi: 10.1007/s00415-016-8381-z.	Publication	Negative
Marin, S. E. *et al.* (2013) 'Leigh syndrome associated with mitochondrial complex I deficiency due to novel mutations In NDUFV1 and NDUFS2', *Gene*. Elsevier B.V., 516(1), pp. 162–167. doi: 10.1016/j.gene.2012.12.024	Publication	Mixed
Marsac, C. *et al.* (1997) 'Biochemical and genetic studies of four patients with pyruvate dehydrogenase E1α deficiency', *Human Genetics*. Hum Genet, 99(6), pp. 785–792. doi: 10.1007/s004390050449.	Publication	Mixed
Martikainen, M. H. *et al.* (2012) 'Successful treatment of POLG-related mitochondrial epilepsy with antiepileptic drugs and low glycaemic index diet', *Epileptic Disorders*. Epileptic Disord, pp. 438–441. doi: 10.1684/epd.2012.0543.	Publication	Positive

Martinelli, D. *et al.* (2012) 'EPI-743 reverses the progression of the pediatric mitochondrial disease-Genetically defined Leigh Syndrome', *Molecular Genetics and Metabolism*. Elsevier Inc., 107(3), pp. 383–388. doi: 10.1016/j.ymgme.2012.09.007.	Publication	Positive
Mayr, J. A. *et al.* (2011) 'Thiamine pyrophosphokinase deficiency in encephalopathic children with defects in the pyruvate oxidation pathway', *American Journal of Human Genetics*. Am J Hum Genet, 89(6), pp. 806–812. doi: 10.1016/j.ajhg.2011.11.007.	Publication	?
McFarland, R. *et al.* (2004) 'De Novo Mutations in the Mitochondrial ND3 Gene as a Cause of Infantile Mitochondrial Encephalopathy and Complex I Deficiency', *Annals of Neurology*, 55(1), pp. 58–64. doi: 10.1002/ana.10787.	Publication	Mixed
McWilliam, C. A. *et al.* (2010) 'Pyruvate dehydrogenase E2 deficiency: A potentially treatable cause of episodic dystonia', *European Journal of Paediatric Neurology*. Elsevier Ltd, 14(4), pp. 349–353. doi: 10.1016/j.ejpn.2009.11.001	Publication	Positive
Montini, G., Malaventura, C. and Salviati, L. (2008) 'Early Coenzyme Q10 Supplementation in Primary Coenzyme Q10 Deficiency', *New England Journal of Medicine*, 358(26), pp. 2849–2850. doi: 10.1056/nejmc0800582.	Publication	Positive
Naito, E. *et al.* (1997) 'Biochemical and molecular analysis of an X-linked case of Leigh syndrome associated with thiamin-responsive pyruvate dehydrogenase deficiency', *Journal of Inherited Metabolic Disease*, 20(4), pp. 539–548. doi: 10.1023/A:1005305614374.	Publication	Positive
Naito, E. *et al.* (2002) 'Thiamine-responsive pyruvate dehydrogenase deficiency in two patients caused by a point mutation (F205L and L216F) within the thiamine pyrophosphate binding region', *Biochimica et Biophysica Acta - Molecular Basis of Disease*. Biochim Biophys Acta, 1588(1), pp. 79–84. doi: 10.1016/S0925-4439(02)00142-4.	Publication	Positive
Naito, E. *et al.* (2002) 'Diagnosis and molecular analysis of three male patients with thiamine-responsive pyruvate dehydrogenase complex deficiency', *Journal of the Neurological Sciences*, 201(1–2), pp. 33–37. doi: 10.1016/S0022-510X(02)00187-9.	Publication	Positive
Ortigoza-Escobar, J. D. *et al.* (2017) 'Thiamine deficiency in childhood with attention to genetic causes: Survival and outcome predictors', *Annals of Neurology*, 82(3), pp. 317–330. doi: 10.1002/ana.24998.	Publication	Positive
Ortigoza-Escobar, J. D. *et al.* (2016) 'Free-thiamine is a potential biomarker of Thiamine transporter-2 deficiency: A treatable cause of Leigh syndrome', *Brain*, 139(1), pp. 31–38. doi: 10.1093/brain/awv342.	Publication	Positive
Ortigoza-Escobar, J. D. *et al.* (2014) 'Thiamine transporter-2 deficiency: Outcome and treatment monitoring', *Orphanet Journal of Rare Diseases*, 9(1), pp. 1–10. doi: 10.1186/1750-1172-9-92.	Publication	Mixed
Panetta, J., Smith, L. J. and Boneh, A. (2004) 'Effect of high-dose vitamins, coenzyme Q and high-fat diet in paediatric patients with mitochondrial diseases', *Journal of Inherited Metabolic Disease*, 27(4), pp. 487–498. doi: 10.1023/B:BOLI.0000037354.66587.38.	Publication	Mixed
Quinonez, S. C. *et al.* (2013) 'Leigh syndrome in a girl with a novel DLD mutation causing E3 deficiency', *Pediatr Neurol. 2013*, 48(1), pp. 67–72. doi: 10.1016/j.pediatrneurol.2012.09.013.Leigh.	Publication	?
Quintana, E. *et al.* (2009) 'PDH E1β deficiency with novel mutations in two patients with Leigh syndrome', *Journal of Inherited Metabolic Disease*, 32(SUPPL. 1), pp. 339–343. doi: 10.1007/s10545-009-1343-1.	Publication	Positive
Riley, L. G. *et al.* (2017) 'A SLC39A8 variant causes manganese deficiency, and glycosylation and mitochondrial disorders', *Journal of Inherited Metabolic Disease*, 40(2), pp. 261–269. doi: 10.1007/s10545-016-0010-6.	Publication	Positive
Rokicki, D. *et al.* (2017) '3-Methylglutaconic aciduria, a frequent but underrecognized finding in carbamoyl phosphate synthetase I deficiency', *Clinica Chimica Acta*, 471(February), pp. 95–100. doi: 10.1016/j.cca.2017.05.023.	Publication	Mixed

Rubio-Gozalbo, M. E. *et al.* (1999) 'Proton MR spectroscopy in a child with pyruvate dehydrogenase complex deficiency', *Magnetic Resonance Imaging*, 17(6), pp. 939–944. doi: 10.1016/S0730-725X(99)00002-8	Publication	Positive
Salviati, L. *et al.* (2012) 'Haploinsufficiency of COQ4 causes coenzyme Q10 deficiency', *Journal of Medical Genetics*. J Med Genet, 49(3), pp. 187–191. doi: 10.1136/jmedgenet-2011-100394.	Publication	Positive
Satogami, K. *et al.* (2017) 'Schizophrenia-like symptoms in a patient with Leigh syndrome', *Asian Journal of Psychiatry*. Elsevier B.V., 25, pp. 249–250. doi: 10.1016/j.ajp.2016.12.012	Publication	Positive
Scalais, E. *et al.* (2013) 'Early myoclonic epilepsy, hypertrophic cardiomyopathy and subsequently a nephrotic syndrome in a patient with CoQ10 deficiency caused by mutations in para-hydroxybenzoate-polyprenyl transferase (COQ2)', *European Journal of Paediatric Neurology*. Elsevier Ltd, 17(6), pp. 625–630. doi: 10.1016/j.ejpn.2013.05.013.	Publication	Negative
Schiff, M. *et al.* (2006) 'Leigh's disease due to a new mutation in the PDHX gene', *Annals of Neurology*, 59(4), pp. 709–714. doi: 10.1002/ana.20818.	Publication	Positive
Shayota, B. J. *et al.* (2019) 'Case report and novel treatment of an autosomal recessive Leigh syndrome caused by short-chain enoyl-CoA hydratase deficiency', *American Journal of Medical Genetics, Part A*, 179(5), pp. 803–807. doi: 10.1002/ajmg.a.61074	Publication	Positive
Singhi, P. *et al.* (2012) 'Pyruvate Dehydrogenase-E1a Deficiency Presenting as Recurrent Demyelination: An Unusual Presentation and a Novel Mutation', *JIMD Reports*, 4, pp. 107–111. doi: 10.1007/8904.	Publication	Positive
Siu, V. M. *et al.* (2010) 'Amish microcephaly: Long-term survival and biochemical characterization', *American Journal of Medical Genetics, Part A*. Wiley-Liss Inc., 152(7), pp. 1747–1751. doi: 10.1002/ajmg.a.33373	Publication	Positive
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van Dongen, S. *et al.* (2015) 'Thiamine-Responsive and Non-responsive Patients with PDHC-E1 Deficiency: A Retrospective Assessment', *JIMD Reports*, 15, pp. 13–27. doi: 10.1007/8904.	Publication	Mixed
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Yamada, K. *et al.* (2010) 'A wide spectrum of clinical and brain MRI findings in patients with SLC19A3 mutations', *BMC Medical Genetics*. BMC Med Genet, 11(1). doi: 10.1186/1471-2350-11-171	Publication	Negative
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Open-Label, Dose-Escalating Study Assessing Safety, Tolerability, Efficacy, of RP103 in Mitochondrial Disease (MITO-001)	Clinicaltrails.gov	Terminated early
A Long-term Extension of Study RP103-MITO-001 (NCT02023866) to Assess Cysteamine Bitartrate Delayed-release Capsules (RP103) in Children With Inherited Mitochondrial Disease	Clinicaltrails.gov	Terminated early

Supplementary file 3: Leigh syndrome treatabolome