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Literaturübersicht für die 3. Revision der GA1-Leitlinie; Zeitraum 2016-2021 (alphabetische Reihenfolge)

Einteilung des Evidenzniveaus nach SIGN:

Level 1++. Hochwertige Meta-Analysen, systematische Reviews von randomisierten, kontrollierten Studien (RCT) oder RCT mit einem sehr niedrigen Bias-Risiko

Level 1+. Gut durchgeführte Meta-Analysen, systematische Reviews von randomisierten, kontrollierten Studien (RCT) oder RCT mit einem niedrigen Bias-Risiko

Level 1-. Meta-Analysen, systematische Reviews von randomisierten, kontrollierten Studien (RCT) oder RCT mit einem hohen Bias-Risiko

Level 2 ++. Hochwertige systematische Reviews von Case/Control- oder Kohortenstudien
Hochwertige Case/Control- oder Kohortenstudien mit einem sehr niedrigen Risiko für Confounder-Effekt oder Bias und mit der hohen Wahrscheinlichkeit für eine kausalen Beziehung

Level 2+. Gut durchgeführte Case/Control- oder Kohortenstudien mit einem niedrigen Risiko für Confounder-Effekt oder Bias und mit der mittleren Wahrscheinlichkeit für eine kausalen Beziehung

Level 2 -. Case/Control- oder Kohortenstudien mit einem hohen Risiko für Confounder-Effekt oder Bias und mit einem signifikanten Risiko, dass die dargestellte Beziehung nicht kausal ist.

Level 3. Nicht-analytische Studien, z. B. Einzelfallberichte, Fallserien.

Level 4. Expertenmeinung

Author	Title	Study Design	Patients (n)	Clinical endpoints	Results / Conclusions	Bias (according to GRADE)	Confounding (according to GRADE)	SIGN Level	Group (Diagnostik, Therapie, Monitoring)
Abdul Wahab et al. (2016) Biomed Res Int; 2016:4074365	Clinical and Mutational Analysis of the GCDH Gene in Malaysian Patients with Glutaric Aciduria Type 1	Case series	n=7	Clinical outcome Neuroimaging Mutation analysis	Clinical outcome: all patients were symptomatic, onset at age 3 to 11M (n=3 with acute onset, n=2 with insidious onset, n=2 with SDH), age at diagnosis 6M to 13Y. Symptoms: severe motor disability + absence of speech (n=5 patients), moderate disability + ability to walk with assistive device + normal school with educational support (n=1), mild motor impairment (n=1, age 2Y). Neuroimaging: widening of bilateral Sylvian fissures with frontotemporal atrophy in all patients (except 1 patient with generalized cerebral atrophy). Treatment: Upon diagnosis in all patients: low protein diet supplemented with lysine / tryptophan-free synthetic formula and L-carnitine. n=3 novel mutations (Gln76Pro, Glu131Val, Gly390Trp). n=8 missense mutations (Gln76Pro, Glu131Val, Ala298Thr, Gly354Ser, Arg355Cys, Arg386Gln, Gly390Trp, Ala421Thr), n=1 nonsense mutation (Arg128*), n=1 splice site mutation (c.1244-2A>C). n=2 homozygous (Gln76Pro, Arg386Gln) in patients with parental consanguinity. All mutations were predicted to be disease causing by MutationTaster2.	Detection bias (low n)	Indirectness (population differences)	2-	Diagnostik

Abid et al. (2021) Ann Emerg Med 17:S0196-0644(21)00298-5	Risk of Traumatic Brain Injuries in Infants Younger than 3 Months With Minor Blunt Head Trauma	Secondary analysis of public use data set from PECARN's prospective observational study	n=1081 patients <3 months old	Traumatic brain injury after minor head trauma	➔ " The PECARN traumatic brain injury low-risk criteria accurately identified infants <3 months old at low risk of clinically important traumatic brain injuries. However, infants at low risk for clinically important traumatic brain injuries remained at risk for traumatic brain injuries on CT, suggesting the need for a cautious approach in these infants. "	No patients with GA1 included	Indirectness (population differences)	2-	Monitoring
Alaei et al. (2020) Iran Biomed J. 2020 May;24(3):201-5	Once in a Blue Moon, a Very Rare Coexistence of Glutaric Acidemia Type I and Mucopolysaccharidosis Type IIIB in a Patient	Case report	n=1	Mutation analysis	- 4Y boy with first-cousin parents. - Symptoms: Macrocephaly, developmental delay, speech problem, complaints of hyperactivity and concentration problem, falling down when walking, turricephaly, hepatomegaly, wrist weakness, prolonged diarrhea, broad nasal bridge, low-set ears, short palate, macular edema, short Achilles tendons. - 5M: bilateral arachnoid cysts in temporal lobes with extension to Sylvian fissure and increased subarachnoid space over convexities. - 14M: trauma → number of spoken words decreased - two homozygous likely pathogenic variants in NAGLU (c.625A>C; p.Thr209Pro) and GCDH (c.1298C>T; p.Ala433Val) genes confirmed coexistence of GA1& MPSIIIB.	Detection bias (small sample size)	Indirectness (population differences)	3	Diagnostik
Astrand et al (2016) BMC Med; 14:33.	Scandinavian Neurotrauma C. Scandinavian guidelines for initial management of minor and moderate head trauma in children	Guideline	Review		Minor head trauma (80-90%) = Oberbegriff für minimal & mild (& moderate) head trauma (s.u.) ➔ *Patients with mild head injury + normal neurological examination + initial head CT without any pathological findings related to the head trauma can be discharged (Evidence grade: low evidence, Recommendation: weak)"*	No patients with GA1 included		2++	Monitoring
Bekiesinska-Figatowska et al. (2021) BMC	Increasing the spectrum of white matter diseases with tigroid	Case report	N=1	MR imaging	Patient with glutaric aciduria, identified by metabolic workup due to developmental delay. Follow-up over 9 years. Appropriate diet and	Detection bias (small sample size)	Case report	3	Monitoring

Pediatrics; 21:146	pattern on MRI: glutaric aciduria type 1 – case report				supplementation, deficits in specific cognitive skills. 3 MR scans at 8M, 21M, 10Y. Scan 1+2: diffusion restriction in the fornix. Scan 3: "tigroid pattern": radially oriented stripes of low (relatively normal) signal intensity are observed within diffusely affected T2-hyperintense cerebral white matter.		Imprecision (low n of patients)		
Bernstein et al. (2020) Nutrients ; 12 :3162.	Inconsistencies in the Nutrition Management of Glutaric Aciduria Type 1: An International Survey	22-question survey	0 (n=300 health care professionals were asked to respond to the questions, n=66 participated)	Nutrition management	66 dietitians responded, - of which 58 practice in the US / 18 outside of the US; - 57 manage patients identified by NBS, 40 after striatal injury, 26 with late-onset GA1. 1. <6Y, identification through NBS. - Breastfeeding: clinicians allowed feeding at the breast (50%), expressed breastmilk (20%), did not recommend (10%), other (20%). - Medical food: recommended by 87%. 13% did not recommend formulations containing amino acids of which 63% recommended protein restricted diet and 37% did not recommend any restriction (n=3 clinicians). - Counting intact protein: 76% count grams of protein from food, 20% count mg of lysine. 6% use "exchange" system. (patient-dependent: start with counting lysine, later countin protein). - Arginine supplementation: not recommended by 95%. 2. Diet liberalization - Definition: "some restriction of food protein to provide the US dietary reference intake" (84%), reduction/elimination of medical food (46%/30%). No restriction of food protein (7%). - Age of diet liberalization: after age 6Y (27% with striatal injury; 45% without striatal injury); age 3Y (2%/2%); age 10Y (9%/12%); Never (20%/9%). - Protein-controlled diet: providing only the amount recommended by the US DRI (85%), certain amount of protein counted by the patient	Only US, and South American Centers included (selection bias) No Amino acid data reported Different opinions on and implementation of "protein-controlled diet"	Questionnaire	3	Monitoring

					(44%), meat / high biological value protein not allowed (27%). - Tracking protein intake: counting grams of protein (63%), counting "servings" of higher protein foods (20%), no counting at all / full liberalization (20%); depending on patient (7%). - Goals for plasma lysine concentration: before age 6Y low-normal (46%), after age 6Y normal (84%). - Diet monitoring: monitoring of plasma amino acids (before age 6Y 93%, after age 6Y 92%), anthropometrics (91%/ 88%), plasma 3OHGA (9% / 12%), neurocognitive status (23% / 34%).				
Bessey et al. (2020) Int J Neonatal Screen., 6:93	The Cost-Effectiveness of Expanding the UK Newborn Bloodspot Screening Programme to Include Five Additional Inborn Errors of Metabolism	Decision-tree model with lifetable estimates of outcomes, model structure and parameterisation informed by a systematic review and expert clinical judgment.		- National Health Service/Personal Social Services perspective - lifetime costs and quality-adjusted life years (QALYs) were discounted at 1.5%. - Uncertainty in the results was explored using expected value of perfect information analysis methods together with a sensitivity analysis using the screened incidence rate in the UK from 2014 to 2018.	The model estimates that screening for all the conditions is more effective and cost saving when compared to not screening for each of the conditions, and the results were robust to the updated incidence rates	)	key uncertainties: sensitivity and specificity of the screening test and the estimated costs and quality	3	Diagnostik
Biasucci et al. (2018) Ital J Pediatr; 44(1):8	Early neonatal Glutaric aciduria type I hidden by perinatal asphyxia: a case report	Case report	n=1	Perinatal asphyxia Early post-natal onset of GA1	Male patient, born at term after prolonged labour. Severe asphyxia + asystoly soon after birth → cardiopulmonary resuscitation. 30 min after birth severe + diffuse axial hypotonia, increased muscular tone of the limb extremities, absence of crying + archaic reflexes. 90 min after birth: stuporous state with fixed gaze + epileptic	Detection bias (small sample size)	Imprecision (small sample size)	3	Diagnostik

					seizures interrupted by Phenobarbital (recurrent on the first day of life). Diagnosis of GA1 at d10 (enzyme activity + mutation analysis). Start of metabolic treatment (low lysine diet, lysine-free tryptophan-reduced infant formula, supplementation of riboflavin + L-carnitine). Severe encephalopathy with drug resistant epileptic seizures. CVC-related sepsis → exitus at 2y				
Boucherau and Schiff (2020) J Nutr 150 :2556S-2560S	Inherited Disorders of Lysine Metabolism: A Review	Review	0	Glutaric aciduria Antiquitin deficiency	Literature review of inherited disorders of lysine metabolism			3	
Boy et al. (2017) Orphanet J Rare Dis; 12(1):77	Extrastriatal changes in patients with lateonset glutaric aciduria type I highlight the risk of long-term neurotoxicity	Prospective multicentre observational trial	n=8 patients with late-onset GA1 + n=8 early-diagnosed patients with GA1 (=controls)	MRI: (1) frontotemporal hypoplasia, presence of abnormal (2) gray and/or (3) white matter signal, (4) space-occupying lesions	Progredient extrastriatal abnormalities in late onset patients (1) In all late-onset patients, in 3 controls (HE) (2) no patient with typical striatal changes. (3) in all late-onset patients, in 3 controls (HE) (4) in 6 late-onset patients (all patients except maternal GA1), 1 control	Detection bias (small sample size)	Small sample (Imprecision)	2-	Monitoring
Boy et al. (2017) J Inherit Metab Dis; 40(1):75-101	Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: second revision	Guideline		Diagnostic approach Treatment Monitoring	18 recommendations and 5 statements			2++	Diagnostik Therapie Monitoring
Boy et al. (2018) Ann Neurol; 83(5):970-979	Newborn Screening: A Disease-Changing Intervention for Glutaric Aciduria Type 1	Prospective multicentre observational trial	n=94 patients: 87 identified by NBS (64 HE, 21	- Incidence of GA1 in Germany & sensitivity of NBS - Genotype-Phenotype-Correlation	Estimated incidence: 1:124.930 newborns, sensitivity of NBS: 95,6%. Confirmation of diagnosis: Positive NBS results were confirmed by GCDH gene analysis and/or enzyme activity analysis in 80/87 patients	Low risk. Large sample, 98% of patients identified by NBS in	Max. age at last visit: 17,75Y Small sample of older children	2++	Diagnostik Therapie

			LE, 2 unknown), 4 missed by NBS (all LE), 3 maternal GA1 (all HE).	- Neurologic outcome separated into 2 categories: 1. Major motor symptoms (manifestation of a movement disorder) 2. Minor motor symptoms (fine motor deficits and/or delayed achievement of motor milestones) - Maintenance treatment (MT) and intermittent emergency treatment (ET) - Renal outcome: GFR according to Schwartz - Survival	<u>Genotype-Phenotype-Correlation (76 patients):</u> n=35 homozygous (32 HE, n=9 p.Glu365Lys, n=5 p.Arg402Trp), n=38 compound heterozygous (20 HE, 16 LE). Genotype predicts biochemical phenotype, but clinical phenotype is not predicted by genotype or biochemical phenotype. <u>Treatment:</u> n=74 (85%) followed by smc, n=59 (68%) treated according to guideline recommendations. MT including carnitine supplementation resulted in best neurologic outcome. MT deviations comprised: Non-adherence to diet (n=8), inadequate dietary prescription (n=6), feeding problems (n=1), delayed start of MT (n=1). <u>Neurologic outcome:</u> n=56 (64%) asymptomatic, n=31 (36%) neurologic symptoms (n=26 (30%) major motor symptoms (MD), n=5 (6%) minor motor symptoms). Polyneuropathy: n=0 patients. <u>Major motor symptoms:</u> n=13 acute onset (n=11 following EC, n=2 after SDH), n=12 insidious, n=1 unknown. Less severe dystonia in patients with insidious onset. <u>Impact of treatment on outcome:</u> Major motor symptoms: all patients without AET develop MD, 93% with adequate treatment remain asymptomatic. Non-adherence to MT (n=16): 50% dystonia (less severe, high frequency of insidious onset) plus 25% with minor motor symptoms. <u>CKD:</u> Median GFR 123 (range 85-214). N=3/6 Pat. >12Y: GFR <90, N=2 intermitt. GFR <60. N=1 acute renal failure through HUS. → GFR declined with age regardless of neurologic phenotype, did not differ between HE / LE patients or treatment groups. <u>Survival</u>: n=82 (93%) patients survived. 4/5 patients who died had dystonia (n=3 severe, n=1 moderate) following EC, 1 died during HUS. Lower	Germany during 1999-2016 are included.	Invasive infection with pneumococcus + HUS		Monitoring

					life expectancy for patients with severe MD / acute onset MD. Maternal GA1: 2 mothers neurologically asymptomatic				
Boy et al. (2019) J Inherit Metab Dis; 42(1):117-127	Patterns, Evolution, and Severity of Striatal Injury in Insidious-Vs Acute-Onset Glutaric Aciduria Type 1	Case control study	n=21 symptomatic patients: n= 11 acute onset (n=2 LE, n=9 HE), n=10 insidious onset (n=2 with later acute onset) (n=2 LE, n=8HE).	MRI: striatal changes (localized / extensive signal changes, atrophy on visual inspection, new / increasing changes on follow-up) on axial T2-weighted images and analysis of altered diffusion with DWI. Motor outcome.	Median age at onset of dystonia: 10M in both groups. More severe dystonia in patients with acute onset. Striatal lesions: acute-onset (n=11): extensive lesions, insidious-onset (8/10): restricted to dorsolateral putamen, acute-on-insidious (n=2) & insidious with progressive dystonia: extensive striatal changes superimposed on pre-existing dorsolateral putaminal lesions. Latency phase of 3.5 months to 6.5 years between detection and clinical manifestation of dorsolateral putaminal lesions in insidious-onset patients. → pre-symptomatic detection of relevant brain injury → detection of noduli potentially indicating a slow neoplastic process → surrogate of chronic neurotoxicity	no standardized follow-up intervals for MRI	Small sample (Imprecision)	2+	Monitoring
Boy et al. (2021) Genet Med 23: 13-21	Impact of newborn screening and quality of therapy on the neurological outcome in glutaric aciduria type 1: a meta-analysis	Meta-analysis Systematic literature search for articles published from 2000 to 2019 using the PRISMA protocol. Studies reporting on more than one individual	n=647 patients (from 15 publications) Patients identified by NBS vs. patients identified by targeted metabolic studies (diagnosis was made after the	Clinical outcome Neurologic outcome: complex MD with predominant dystonia, or ataxia, or with spastic para- or tetraparesis Onset type: acute / insidious Motor development: normal/abnormal according to age Treatment Mortality	- NBS group: 261 patients (n=171 HE, 53 LE, 37 unknown), TMS group: 386 patients (n=167 HE, 87 LE, 132 unkown) Motor development: patients identified by NBS showed a significantly higher proportion of normal motor development than TMS patients, TMS patients showed a higher rate of delayed motor development. - NBS group: 74,7% asymptomatic, 25,3% MD (n=66 patients, with n=39 acute onset, n=23 insidious onset), neurologic outcome did not differ between HE and LE patients, 9 patients died (7 with severe MD). - TMS group: 9,6% with unspecific clinical signs at diagnosis (without irreversible neurologic symptoms) vs. 90,4 % symptomatic with MD at diagnosis (69,9% acute onset, 22,6% insidious onset, 7,5% unknown onset); 81,7% with delayed		Heterogeneous data quality and number of reported variables Small sample sizes of included studies (in most cases).	1+	Therapie Monitoring

		identified by NBS were included.	onset of clinical symptoms)		motor development, 18,1% of symptomatic patients died. <u>Treatment:</u> Patients not following maintenance treatment (low lysine diet and carnitine supplementation) guideline recommendations showed a trend for increased relative risk for insidious onset MD (complex movement disorder) compared to patients with recommended dietary treatment. - MT according to guideline recommendations in 71,8% (whole NBS group) vs. 51,5% (symptomatic NBS patients) and 49,6% (symptomatic TMS patients) vs. 29,7% (asymptomatic TMS patients). - ET according to guideline: 66,6% (asymptomatic NBS patients) vs. 72,7% (symptomatic NBS patients); data not available for TMS patients. → motor development was more often normal in NBS patients than in TMS patients, with a lower frequency of MD → survival did not differ between NBS and TMS patients → trend for increased relative risk for insidious onset MD in patients not following MT recommendations → increased relative risk for acute onset MD in patients with delayed ET				
Boy et al. (2021) J Inherit Metab Dis 1-10. doi:10.1002/jimd.12436	Subdural hematoma in glutaric aciduria type 1: High excreters are prone to incidental SDH despite newborn screening	Retrospective evaluation for SDH, as part of the ongoing prospective study on long-term outcome of GA1 patients	N=69 patients with 168 MRI scans	Retrospective evaluation for SDH	168 MRIs of 69 patients with GA1 (age at MRI 9 days – 73.8 years, median 3.2 years) - SDH in 8 HE patients, imaged between 5.8 and 24.4 months → space-occupying SDH in 2 patients after minor accidental trauma → SDH as an incidental finding in 6 patients without trauma - patients without trauma imaged at 3 to 30 months (n = 36, 25 NBS, 27/9 high/low excreters): incidence of SDH was 16.7% (16% in NBS). → SDH was more common after acute (33.3%) than insidious onset of dystonia (14.3%) or in asymptomatic patients (5.9%)	no standardized follow-up intervals for MRI	Retrospective design of the study Imprecision (low n)	2+	Monitoring

					→ SDH was only seen in patients with wide frontoparietal CSF spaces and frontotemporal hypoplasia. → HE were over-represented among patients with SDH (6/27 vs 0/9 low excreters), acute onset (10/12), and wide frontoparietal CSF spaces (16/19). ➔ Incidental SDH occurs despite NBS and early treatment in approximately one in six patients with GA1 imaged during late infancy and early childhood. Greater risk of high excreters is morphologically associated with more frequent enlargement of external CSF spaces including frontotemporal hypoplasia, and may be furthered aggravated by more pronounced alterations of cerebral blood volume and venous pressure.				
Campos-Garcia et al. (2019) Mol Genet Metab Rep; 21:100533	Characterization of novel GCDH pathogenic variants causing glutaric aciduria type 1 in the southeast of Mexico	Case series	n=5	Mutation analysis	n=3 novel mutations: c.389T>C, c.1108delC, c.1172G>T <u>Patient 1:</u> compound heterozygous (c.880C>T + c.881G>A). <u>Patient 2+4:</u> homozygous (c.389 T>C). <u>Patient 3:</u> compound heterozygous (c.389T>G + c.1108delC) <u>Patient 5:</u> compound heterozygous (c.389T>C + c.1172G >T)	Detection bias (small sample size)	Indirectness (population differences)	2-	Diagnostik
Carling et al. (2020) Int J Neonatal Screen 6:92	Evaluation of a Common Internal Standard Material to Reduce Inter-Laboratory Variation and Ensure the Quality, Safety and Efficacy of Expanded Newborn Screening Results When Using Flow Injection Analysis Tandem Mass	Methodology		Evaluation of the effect of stable isotope internal standard (IS) used for quantitation on inter-laboratory variation	NBS programs in England and Wales now include four additional disorders: classical homocystinuria, IVA, GA1, MSUD. Post-implementation, population data monitoring showed high inter-laboratory variation with 90th centiles varying from 17% to 59%. → Four laboratories analysed routine screening samples (n > 101,820) using a common IS. Inter-laboratory variation was determined for the eight analytes and compared with results obtained using an in-house common IS (n > 102,194). A linear mixed-effects model was fitted to the data. → Using a common IS mix reduced the inter-laboratory variation significantly ($p < 0.05$) for five analytes. For three analytes, the lack of		Indirectness (population differences)	2-	Diagnostik

	Spectrometry with Internal Calibration				significance was explained by use of individual laboratory "calibration factors". ➔ For screening programs where laboratories adhere to single analyte cut-off values (COVs), it is important that inter-laboratory variation is minimized, primarily to prevent false positive results. Whilst the use of a common IS helps achieve this, it is evident that instrument set-up also contributes to inter-laboratory variation.				
Chen et al. (2020) Orphanet J Rare Dis 15:337	Audiological and otologic manifestations of glutaric aciduria type I	Observational, single center	N=13 (Taiwan) 12/13 NBS and 1/13 TMX, 2-26yrs	Pure tone average (PTA) by calculating the threshold of frequencies at 500, 1000, 2000 and 4000 Hz. no hearing loss = PTA was less than 16 dB HL, 16–25 dB HL was slight hearing loss, 26–40 dB HL was mild hearing loss, 41–55 dB HL was moderate hearing loss, 56–70 dB HL was moderately severe hearing loss, 71–90 dB HL was severe hearing loss, and ≥ 91 dB HL was profound hearing loss Neurologic symptoms Molecular genetic testing including targeted sequencing of 4 common genes related to deafness	3/13 had EC 2/13 seizure Sensineural hearing loss in 76.9% (10/13), slight: n=6, mild: n=2, moderate: n=1 N=3 EC patients, not significant on hearing loss ICU Patients (6/13) significantly more hearing loss (only significant risk factor variable) 4/13 asymptomatic patients without EC (#1, 2, 7, 12) had slight-mild hearing loss (2/4 had ICU treatment, ¼ had increased disability score after ICU) MRI did not detect abnormal ENT causes Macrocephaly had no impact on hearing function	Retrospective analysis Single center	Small study sample (Imprecision) Treatment and treatment compliance not reported Classification of symptomatic patients unclear 1 asymptomatic had EC? 1 asymptomatic had basal ganglia diffusion abnormality? 1 seizure patient had EC, but no dystonia?	2-	Monitoring

				MRI					
Cornelius et al. (2021) Ann Indian Acad Neurol 24: 22-26	Pediatric Glutaric Aciduria Type 1: 14 Cases, Diagnosis and Management	Case series	N=14	Diagnosis Clinical presentation	- mean age at onset of symptoms: 8.57 ± 3.57 M - mean age at diagnosis: 35.21 ± 48.31 M. - consanguinity: 57.1% - normal development prior to the onset of acute crises in 75% - Acute crises triggered by infection followed by the regression of milestones was the major presenting feature in 10 children (71.4%). - Macrocephaly: 10 children. - Bat's wing appearance (fronto temporal atrophy) in all children. - dystonic movement disorder and spastic quadriparesis with moderate to severe disability in 80%		Imprecision (Small sample size) Indirectness (population differences)	3	Diagnostik
David et al. (2019) Cent Eur J Public Health; 27 (2): 153–159	EPIDEMIOLOGY OF RARE DISEASES DETECTED BY NEWBORN SCREENING IN THE CZECH REPUBLIC	Case series	n=5	Prevalence of rare diseases Diagnostic criteria	Prevalence = 1 : 177,778 Limits dried blood spots: C5DC > 0.40 (0.60) µmol/L, C5DC/C8 ratio > 5.40 (C5DC/C16 > 0.40) Confirmation: C5DC + C8 + C16 above reference range + GCDH deficiency or 2 pathogenic mutations in GCDH gene	Detection bias (small sample size)	Indirectness (population differences) Imprecision (Small sample size)	3	Diagnostik
Del Rizzo et al. (2016) Eur J Pediatr ; 175:1123–1128	The long-term treatment of a patient with type 1 diabetes mellitus and glutaric aciduria type 1: the effect of insulin	Case report	n=1: 21M male	Coexistence of type 1 diabetes mellitus and GA1 in one patient	- Diagnosis of type 1 diabetes mellitus at age 15M, with a tendency towards hypoglycemia. - Diagnosis of GA1 at age 21M due to acute hypotonia of the limbs and limbs dystonia during an acute intercurrent infective episode. - Mutation analysis: c.656C>A, c.1198G>A. - Treatment: low-lysine diet, carnitine supplementation. -Nasogastric tube due to swallowing difficulties, severe hypoglycemic episodes during the first week of treatment. → Long-term follow-up suggests protective role of insulin treatment in preventing GA1 metabolic decompensation + positive role of GA1 metabolic balance toward glycemic equilibrium → Systematic evaluation of glycemic profile in patients with IEMs to detect hypoglycemic episodes +	Detection bias (small sample size)	Imprecision (small sample size)	3	Diagnostik Therapie

					→ Possible improvement of outcome with adequate glucose homeostasis after the diagnosis of IEMs (including insulin treatment under specific conditions). → Careful differential monitoring of glomerular + tubular renal function ist recommended.				
Du Moulin et al. (2018) JIMD Rep; 39:25-30	Glutaric Aciduria Type 1 and Acute Renal Failure: Case Report and Suggested Pathomechanisms	Case report	n=1: 3Y female diagnosed with GA1 by NBS (HE), asymptomatic till infection, no MD, no developmental deficits	Haemolytic uraemic syndrome + acute renal failure	- HE (Urinary GA: 2650 mmol/mol creatinine) - <u>Mutation analysis:</u> homozygous p.Arg402Trp - Treatment: Lysine-restricted diet + carnitine + ET - <u>Normal clinical course</u> until age 3Y - Febrile airway infection in Turkey at 3;3Y with dyspnea - Reduced consciousness + haematemesis on the way to the hospital. - Somnolence, fever, tachypnea, severe metabolic acidosis at admission, no MD, ET started. - Diagnosis of invasive septic infection with Streptococcus pneumoniae + start of antibiotic treatment. - Acute renal failure (creatinine 1,68 mg/dL, renal US: bilateral swelling, cortical hyperchogenicity, subcortical hypofusion), haemolytic anaemia, thrombocytopenia → <u>atypical haemolytic uraemic syndrome associated with pneumococcal disease.</u> - Peritoneal dialysis (from d3), then hemodialysis (from d6). - <u>No clinical signs of MD at any time,</u> cranial CT without abnormalities of basal ganglia. - Severe lactic acidosis, refractory to any therapeutic intervention. - Death at d22 after admission due to multiple organ failure. → Endothelial dysfunction + renal proximal tubule accumulation of GA1 metabolites may contribute to acute + chronic glomerular + tubular dysfunction in GA1 patients.	no biopsy conducted, no MRT (only CT d13), no immunologic diagnostics delayed intensive care (somnolent at admission, start of disease in Turkey?)	Only two cases in literature to date	3	Monitoring
El Fotoh et al. (2019) CNS Neurol Disord Drug Targets; 18(5):413-420	Autism Spectrum Disorders: The Association with Inherited Metabolic	Retrospective study, case report	n=320 patients with Autism Spectrum	Etiologic Workup of Autism Spectrum Disorders	8Y male - Diagnosis of Autism Spectrum Disorder due to delayed speech + difficulty with sozialisation.	Detection bias (small sample size)	Retrospective study Only one patient with GA1		Diagnostik

	Disorders and Some Trace Elements. A Retrospective Study		Disorders, of which n=1 with GA1		- Mentally retarded, lack of interest in surroundings, stereotypical movements. Normal physical examination. - MRI brain + organic acids in urine characteristic for GA1. - Treatment: Oral riboflavin, oral coenzyme Q10, L-carnitine, tryptophan-lysine-restricted diet. → Patients with Autism Spectrum Disorders should be screened for Inherited Metabolic Disorders + trace elements.				
Fehlings et al. (2018) Dev Med Child Neurol, 60: 356-366	Pharmacological and neurosurgical interventions for managing dystonia in cerebral palsy: a systematic review	Systematic review	(28 articles)	- Managing dystonia in individuals with cerebral palsy - Motor function - Pain, comfort	→ For dystonia reduction intrathecal baclofen and deep brain stimulation are possibly effective, trihexyphenidyl is possibly ineffective. → Insufficient evidence to support oral medications or botulinum toxin to reduce dystonia. → Insufficient evidence for pharmacological and neurosurgical interventions to improve motor function, decrease pain etc.	selection bias: cohort consists of patients with dystonic CP, not GA1; heterogenous group		1-	Therapie
Foran et al. (2021) JIMD Reports 58:12-20	Low excretor glutaric aciduria type 1 of insidious onset with dystonia and atypical clinical features, a diagnostic dilemma	Case report	N=1	Clinical presentation Diagnostic procedure	4Y female - Referred for reassessment of dyskinetic cerebral palsy - MRI brain: bilateral putamen hyperintensity - generalized dyskinesia predominantly bulbar and limbs - Motor and speech development most affected, preservation of cognitive development - no history of acute encephalopathic crisis or status dystonicus - Initial urine organic acids, amino acids, acylcarnitine profile: normal - dystonia genetic panel: compound heterozygosity (pathogenic variant + variant of uncertain significance in GCDH gene) - repeat urine organic acids: isolated slightly increased 3OHGA excretion - repeat MRI Brain at age 4Y: volume loss, symmetric T2 hyperintensity in posterior putamina bilaterally.	Detection bias (small sample size)	Imprecision (small sample size)	3	Diagnostik

Frenkel et al. (2020) Cureus; 12 (6)	Intrathecal Baclofen for Hypertonia Secondary to Glutaric Aciduria Type I	Case report	n=1: 15Y female	Treatment of Hypertonia with intrathecal baclofen	15Y female diagnosed based on NBS, start of treatment. 2 encephalopathic crises resulting in dystonia and spastic quadriplegic cerebral palsy. - intrathecal baclofen was titrated to 375 µg/d, then following 2 years, she did not need any enteral baclofen or diazepam anymore.	Detection bias (small sample size)	N=1	3	Therapie
Gelener et al. (2020) Neurogenetics. 2020; 10.1007/s10048-020-00610-9	Adult-onset glutaric aciduria type I: rare presentation of a treatable disorder	Case report	n=1: 35Y female	Brain MRI Genetic testing Neuropsychologic testing	-Headache + subjective memory problems, no history of dystonic movement disorders. - Normal neurological exam + neurocognitive tests. Mild stress-related anxiety and depression were reported. - Brain MRI: white matter abnormalities, mild frontotemporal hypoplasia, subependymal nodules located at the border of the lateral ventricles, especially at the roof level, and along the septum pellucidum. Some of the subependymal nodules were cystic. - GA in Urine: 7176 mmol/mol creatinine. - Mutation analysis: c.1204C > T (p.R402W, homozygous) variant in GCDH gene.	Detection bias (small sample size)	N=1	3	Diagnostik Monitoring
Ghatan et al. (2016) Mov Disord Clin Pract; 3(3):296-299	Intraventricular Baclofen for Treatment of Severe Dystonia Associated with Glutaryl- CoA Dehydrogenase Deficiency (GA1): Report of Two Cases	Case series	n=2 patients with intractable generalized dystonia secondary to GA1	Treatment of Severe Dystonia with intraventricular baclofen	Patient 1: 10Y female with generalized dystonia since age 17M (acute onset after EC + diagnosis of GA1). - Intraventricular catheter + abdominal infusion pump placed under general anesthesia, catheter tip placed in third ventricle, baclofen pump placed in infraumbilical abdominal wall, catheter tunneled to incision in right retroauricular region. - 200-220 µg/d Baclofen over 36M post-OP → significant improvement of dystonia (BADS score 30,7 → 5,0). Patient 2: 23Y male with generalized dystonia since age 1Y (acute onset after EC). - Pump placed as described above. - 1665 µg/d Baclofen were needed to improve BADS from 29,7 to 24,3.	Detection bias (small sample size)	Imprecision (small sample size)	3	Therapie
Govender et al. (2017) S Afr Med J; 107(3):201-204	A review of patients with glutaric aciduria type 1 at Inkosi	Case series	n=6	Clinical outcome Mutation analysis Brain MRI	- Mean age at diagnosis: 12M - Symptoms: Encephalopathic crisis (n=4), hypotonia (n=4), macrocephaly (n=5), seizures (n=4), dystonia (n=3), bulbar dysfunction (n=4).		Indirectness (population differences)	3	Diagnostik

	Albert Luthuli Central Hospital, Durban, South Africa				- Mutation analysis: p.A293T (n=5). - Brain MRI: hyperintense basal ganglia, widened perisylvian fissures (all n=6). -Clinical course: static (n=2), gain of milestones (n=1), further neuroregression (n=3).		Imprecision (small sample size)		
Grasemann et al. (2020) Monatsschrift Kinderheilkunde	Ein strukturierter Versorgungspfad von der Pädiatrie in die Erwachsenenmedizin für Jugendliche und junge Erwachsene mit einer seltenen Erkrankung.	Expert opinion/Methodoloy			Standardized strategy for patient care in rare diseases			3	Monitoring
Guerreiro et al. (2018) J Cell Biochem; 119(12):10021-10032.	Oxidative damage in glutaric aciduria type I patients and the protective effects of L-carnitine treatment	3 cohorts: patients at diagnosis, patients under 100 mg/kg/d L-carnitine and patients under protein restricted diet and 100 mg/kg/d L-carnitine, healthy age-matched controls	n=24 patients with GA1, of which n=12 at diagnosis + n=12 under treatment. + n=12 healthy, age-matched controls.	Oxidative and nitrative stress - 15-F2t-isoprostane - Di-tyrosine (Di-tyr) autofluorescence - Oxidized guanine species - Antioxidant capacity - Reactive Nitrogen Species Inflammation profile - Cytokines	- Levels of free L-carnitine of GA1 patients at diagnosis are significantly reduced, normal in patients under treatment. - 15-F2t-isoprostane in urine (marker of lipid peroxidation) + Di-tyr in urine (marker of oxidative stress) + Reactive Nitrogen Species + DNA damage: Increased at diagnosis compared to controls, reduction by treatment. - Antioxidant capacity: Low at diagnosis, normalization under treatment. - Cytokines: patients under treatment presented significantly higher levels of IL-6, GM-CSF, TNF-α, IL-8 compared to controls → Beneficial effects of L-car are due not only by increasing the excretion of accumulated toxic metabolites, but also by preventing oxidative damage.	medium risk due to small sample size; clinical significance of tested parameters unknown	not known	2-	Therapie
Guerreiro, et al. (2019) BBA – Molecular Basis of Disease	L-Carnitine prevents oxidative stress in striatum of glutaryl-CoA	30-day-old Gcdh-/- mice and WT mice were	5-7 mice per group	Analysis of different parameters on oxidative stress in striatum after 72h of diet and 3 L-carnitine injections	Administration of L-carnitine attenuated all aspects of oxidative stress in striatum of ko mice	unknown	No clinical data	2- (experimental animal study)	Therapie

	dehydrogenase deficient mice submitted to lysine overload	submitted to normal diet or high lysine diet and the effect of intraperitoneal administration of L-carnitine versus saline was tested	Ko vs WT, ND vs HLD, saline vs L-carnitine injection (100 mg/kg/d)						
Guerreiro et al. (2020) Int J Dev Neurosci; 80(1):42-49	Elevated levels of BDNF and cathepsin-d as possible peripheral markers of neurodegeneration in plasma of patients with glutaric acidemia type I		n=6 patients with GA1 diagnosed due to clinical symptoms	Peripheral markers of neurodegeneration in plasma of patients with GA1	BDNF, cathepsin-D: Elevated in GA1 patients compared to controls. PDGF-AA, NCAM: No difference between GA1 patients and controls. Correlation with C5DC: High correlation with cathepsin-D	Detection bias (small sample size)	Indirectness (population difference)	2-	Monitoring
Guerreiro et al. (2021) Arch Biochem Biophys 709 : 108970	Protective effects of L-carnitine on behavioral alterations and neuroinflammation in striatum of glutaryl-COA dehydrogenase deficient mice		N=0	striatum of knockout mice (Gcdh− /-) and wild type (WT) mice submitted to a normal or a high Lys diet + potential protective effects of L-carnitin treatment → behavior parameters → pro-inflammatory factors (cytokines IL-1β, TNF-α and cathepsin-D levels) → anti-inflammatory cytokine IL10	- Gcdh− /- mice showed behavioral changes, including lower motor activity (decreased number of crossings) and exploratory activity (reduced number of rearings). - Gcdh− /- mice had significantly higher concentrations of glutarylcarnitine (C5DC) in blood and cathepsin-D (CATD), interleukin IL-1β and tumor factor necrosis alpha (TNF-α) in striatum than WT mice - L-car treatment prevented most behavioral alterations, normalized CATD levels and attenuated IL-1β levels in striatum of Gcdh− /- mice. - IL-1β was positively correlated with CATD and C5DC levels and L-car was negatively correlated with CATD	No clinical data		2-	Pathophysiologie

				in	➔ protective effects of L-car on behavioral changes and pro- inflammatory status in striatum of the animal model of GA1				
Gürbüz et al. (2020) Genetic and phenotypic spectrum in 53 patients. Eur J Med Genet. 2020 Aug 7;63(11):104032	Glutaric aciduria type 1: Genetic and phenotypic spectrum in 53 patients	Descriptive retrospective cross-sectional analysis	n=53	Mutation analysis Clinical presentation	- n=53 patients of 39 unrelated Turkish families, diagnosed between 1998 and 2019. - mean age at diagnosis 4.04Y ± 6.77 (range 0.08 to 41Y). - n= 47 (88.7%) neurologically symptomatic, of which n=44 early-onset (start of symptoms at age <5Y), n=3 late-onset (start of symptoms at age >5Y). - in 3 of 43 patients in whom a trigger of the crisis was known, it occurred after vaccination - n=32 (60.3%) with EC. - n=33 (62.3%) with macrocephaly. - 20 different pathogenetic variants, of which 7 novel (p.Glu57Lys, p.Ser145Profs*79, p.Ser246Glyfs*96 p.Ala293Val, p.His348Gln, p.His417Tyr, p.Asp418Val).		Indirectness (population differences)	2-	Diagnostik Therapie
Hafeez et al. (2019) J Coll Physicians Surg Pak; 29(1):84-86	Dyskinesia in a Child: A Concern for a Rare Neuro-Metabolic Disorder	Case report	n=1: 3Y male patient diagnosed with GA1 due to clinical symptoms	Clinical symptoms	- Symptoms: Progressive macrocephaly, delayed motor milestones. - Diagnosis of GA1, start of treatment with low-lysine diet + carnitine.	Detection bias (small sample size)		3	Diagnostik
Hale et al. (2020) Neurosurg Rev 43, 873–880 (2020)	Deep brain stimulation in pediatric dystonia: a systematic review	Systematic review of retrospective studies	n=76 patients (from 19 studies)	Deep brain stimulation Disease causes + characteristics (incl. mutation analysis) Motor + disability scores	- Mean age at diagnosis 6.91 ± 0.47Y; at surgery 13.8 ± 0.45Y - Etiology: Primary dystonia (n=29 DYT1+, n=23 DYT1-), secondary dystonia (n=24). - DBS treatment: n=69 (91%): bilateral globus pallidus interna (GPi) target, n=1 (1.3%) unilateral GPi implant, n=1 (1.3%) bilateral GPi + subthalamic nucleus (STN), n=5 (6.6%) unilateral GPi implant + contralateral GPi lesion. -Improvement of 43.8 ± 36% in motor scores, 43.7 ± 31% in disability scores.	selection bias: cohort consists of pediatric patients with dystonia (primary and secondary), not GA1; heterogenous group		2++	Therapie

					- Improvement of at least 50% in motor scale was more likely in patients with primary dystonia than in patients with secondary causes of dystonia. - Improvement of at least 50% in disability (not motor) scale was more likely in DYT1+ than in DYT1-.				
Heathfield et al. (2020) Int J Legal Med; 134(5):1639-1645	Assessment of candidate variants causative of inborn metabolic diseases in SUDI cases in South Africa, and a case report	Retrospective study	n=169 cases with sudden unexpected death in infants (SUDI), of which n=4 carried the GCDH mutation c.877G>A/T.	Mutation analysis (post-mortem)	- n=4 cases with heterozygous detection of c.877G>A/T and with no other variant in the rest of the GCDH gene → GA1 was not confirmed.	Selection bias	Only 4 patients with heterogenous GCDH variant, no GA1 patients	3	Diagnostik
Heringer et al. (2016) J Inherit Metab Dis; 39:341–353	Impact of age at onset and newborn screening on outcome in organic acidurias	Observational study	n=567 patients with OADs, of which n=176 patients with GA1	Neurologic outcome	- Median age at diagnosis was significantly lower in patients diagnosed by NBS than by selective screening. - Early diagnosed + treated had better neurologic outcome + achievement of motor milestones + showed more often normal development / less frequent MD.			2+	Diagnostik Therapie
Huishu et al. (2021) Front Genet 12: 702374	Evaluation of the Clinical, Biochemical, Neurological, and Genetic Presentations of Glutaric Aciduria Type 1 in Patients From China	Observational study	N=101	Clinical presentation Mutation Analysis Neurologic phenotype Biochemical phenotype	- 20 patients diagnosed by NBS - 81 identified following clinical intervention - Clinical presentation: Macrocephaly, movement disorders, seizures. - 59 patients evaluated by brain MRI, 58 patients had abnormalities, most common: widening of the sylvian fissures - concentration of glutarylcarnitine in the blood, glutarylcarnitine/ capryloylcarnitine ratio, and urine levels of glutaric acid were increased in GA1 patients and were shown to decrease following intervention. - 88 patient had mutation analysis: 74 variants within the GCDH gene, including 23 novel variants		Indirectness (population differences)	2+	Diagnostik Monitoring

					- most common variant: c.1244-2A > C (18.4%) - no significant differences in biochemical or clinical phenotypes in patients with the four most common variants: c.1244-2A > C, c.1064G > A, c.533G > A, and c.1147C > T. → Patients identified by newborn screening had better outcomes than clinical patients. ➔ expanded NBS using MS/MS could facilitate early diagnosis + treatment and improve clinical outcomes				
Imerci et al. (2020) J Child Orthop; 14.	Orthopaedic manifestations of glutaric acidemia Type 1	Retrospective chart review over 28 years, using institution `s inpatient and outpatient records	n=114 GA1 patients, diagnosed with GA1 during 28 years from 1988 – 2018, mean age at follow-up was 11.9 +/- 9.0 years, most from the Old Order Amish population in Pennsylvania	- demographics, medical comorbidities, muscle tone patterns, Gross Motor Function Classification System level, gastrostomy tube status, seizure history, inpatient events, orthopaedic diagnoses and operative characteristics.	Gross Motor Function Classification System (GMFCS) score: Although 48% of the patients were GMFCS I (normal motor function), 22 % had milder motor problems (GMFCS II or III), primarily patients with severe impairment (GMFCS IV-V) (30%) developed significant orthopedic deformities requiring surgical treatment: - n=24 patients (21%) with musculoskeletal problems requiring orthopaedic consultation, of which - n=14 scoliosis, n=8 hip dislocation, n=2 hip subluxation, n=2 windswept hip deformity in the spine and hip joint. - n=35 orthopaedic surgeries in n=17patients (71%). - none of the patients had normal muscle tone, n=1 was hypotonic, n=15 were dystonic, and 8 had a mixed type.	Performance bias (only symptomatic patients included)	Retrospective chart review	2-	Treatment
Jaumar et al. (2012) Molecular Genetics and Metabolism 106:488-490	Rhabdomyolysis, acute renal failure, and cardiac arrest secondary to status dystonicus in a child with glutaric aciduria type I	Case report	N=1	Status dystonicus	Patients with GA1 and status dystonicus may be at risk for acute life-threatening rhabdomyolysis, renal failure and further neurological injury at any age.		N=1	3	Monitoring

Kaur et al. (2021) Am J Med Genet 185A: 1854-1857	Management of COVID-19 infection in organic acidemias	Case series	N=1 (with GA1, + n=1 with propionic acidemia)	SARS-CoV-2 infection in patients with inborn errors of metabolism	8M female, diagnosed with GA1 by NBS. - no previous hospitalization for metabolic decompensation - fever, increased crying, rhinorrhea, decreased intake of formula, no intake of food. - PCR for SARS-CoV-2 was +, metabolic acidosis - ET started until oral intake improved on day 3, discharged on day 7		Imprecision (Small sample size)	3	Therapie
Kaya Ozcora et al. (2018) JIMD Rep; 38:7-12	Glutaric Acidemia Type 1: A Case of Infantile Stroke	Case report	n=1	Brain MRI Mutation analysis	Case: 9M male with focal tonic-clonic seizures during rotavirus-infection and acute infarction. MRI: acute infarction in bilateral basal ganglia and then extending to the internal capsule genus at the level of the left globus pallidus. Confirmation of diagnosis via mutation analysis (homozygous c. 572T>C, p.M191T). Treatment: protein restricted diet, carnitine + riboflavin supplementation. Follow-up (1y): no metabolic crises, delayed motor + language development. Control-MRI after 29M: loss of volume, T2: increase in left putamen + caudate nucleus, arachnoid cyst in left anterior temporal + frontal lobe.	Detection bias (small sample size)	N=1	3	Diagnostik
Kiykim et al. (2016) Autism Res; 9(2):217-223	Inherited Metabolic Disorders in Turkish Patients With Autism Spectrum Disorders	Case series	n=300 children with Autism Spectrum Disorders, of which n=1 patient was diagnosed with GA1	Autism Spectrum Disorders in Patients with Inherited Metabolic Disorders	5Y male, consanguineous parents, diagnosis of ASD at age 2;6Y due to delayed speech, diminished socialization, hyperactivity. - Brain MRI: symmetrical frontal white matter changes + opercular atrophy. - No mental retardation, normal physical examination except macrocephaly. - Mutation analysis: homozygous c. 263G>A. - Treatment: carnitine, riboflavin, coenzyme Q, tryptophan-lysine restricted diet.	Detection bias (small sample size)	Indirectness (population differences) Only 1 GA1 Patient	3	Diagnostik
Kölker et al. (2015) Journal of inherited metabolic	The phenotypic spectrum of organic acidurias and urea cycle	Cohort study	N=795 (OADs/UCD)		Chronic renal failure in adult and adolescent GA1 patients, independent from motor phneotype			2+	Monitoring

disease 38:1041-1057.	disorders. Part 2: the evolving clinical phenotype								
Kurkina et al. (2020) Metab Brain Dis. 2020; 10.1007/s11011-020-00554-x	Molecular and biochemical study of glutaric aciduria type 1 in 49 Russian families: nine novel mutations in the GCDH gene	Case series	n=51	Mutation analysis Genotype-Phenotype (GA in urine)-correlation	n=9 novel mutations (c.127 + 1G > T, c.471_473delCGA, c.161 T > C (p.Leu54Pro), c.531C > A (p.Phe177Leu), c.647C > T (p.Ser216Leu), c.705G > A (p.Gly235Asp), c.898 G > A (p.Gly300Ser), c.1205G > C (p.Arg402Pro), c.1178G > A (p.Gly393Glu)) n= 53 patients with c.1204C>T, n= 10 patients with c.1262C>T n=1 homozygous for p.Val400Met without biochemical changes	Detection bias (small sample size)	Indirectness (population differences)	2-	Diagnostik
Larson A, Goodman S (2019) In: Adam MP, Ardinger HH, Pagon RA, et al., GeneReviews	Glutaric Acidemia Type 1	Literature review	n=0		Recommended Evaluations Following Initial Diagnosis of GA-1: Developmental assessment: "Consider referral to developmental pediatrician". Delayed acquisition of developmental milestones: Monitor developmental milestones, as needed. Neuropsychological testing using age-appropriate assessment batteries, as needed. Standardizes quality of life assessment tools for affected individuals and parents/caregivers, as needed. Regular evaluations; routine evaluations including amino acids levels 0-12 M: min every 3M 1-6Y: every 6M >6Y: annually			4	Diagnostik Monitoring Therapie
Liow et al. (2016) EJPN	Gabepentin can significantly decrease dystonia severity and quality of life in children	Retrospective monocenter study	69; 3 groups gabapentin plus DBS (21)/ plus comedication (6)/ pure gabapenti	DSAP level dystonia severity assessment plan	Siginificant improvement in function compared to baseline Gabepentin can significantly decrease dystonia severity and quality of life in children		Imprecision (no GA1 patients)	2+	Therapie

			n (33); mean dosage 18 mg/kg						
Lin et al. (2017) Curr Opin Pediatr 29: 652-664.	Advances in pharmacotherapies for movement disorders in children: current limitations and future progress	Review		L-Dopa trial			Imprecision (no GA1 patients)		Therapie
Lin et al. (2021) Orphanet J Rare Dis; 16:339	Biochemical and molecular features of Chinese patients with glutaric acidemia type 1 detected through newborn screening	Case series	N=13 patients with GA1, of whom 11 newborns and 2 maternal GA1 patients	Mutation analysis Biochemical analysis Incidence of GA1	- incidence in Quanzhou region: 1:47,044 newborns - initial NBS results: all but one of the patients had moderate to markedly increased C5DC levels -1 neonatal patient with low free carnitine (C0) level suggest primary carnitine deficiency (PCD) but was ultimately diagnosed as GA1. - 9 neonatal GA1 patients had urinary organic acid analyses: 8 had elevated GA + 3OHGA levels, 1 had normal results - 10 distinct GCDH variants identified, of which 8 were previously reported, 2 newly identified - In silico prediction tools and protein modeling analyses suggested that newly identified variants were potentially pathogenic. - most common variants: c.1244-2 A>C (allelic frequency: 54.55% (12/22)), c.1261G>A (p.Ala421Thr) (9.09% (2/22).)		Indirectness (population differences)	3	Diagnostik
Lisyova et al. (2016) Bratisl Lek Listy; 117(11):631-638	GAI – distinct genotype and phenotype characteristics in reported Slovak patients	Case series	n=2	Mutation analysis Genotype-phenotype-correlation	1: homozygous c.1213dupA (novel) 2: compound heterozygous c.1262C>T + c.1225G>A (novel)	Detection bias (small sample size)	Indirectness (population differences) Unclear patient classification Imprecision (Small sample size)	2-	Diagnostik

Maceda et al. (2020) Acta medica Philippina; 54(4): 387-393	Clinical, Biochemical, and Radiologic Characteristics of Filipino Patients with Glutaric Aciduria Type 1	Case series	n=7	Biochemical parameters, developmental assessment, neurologic assessment, radiologic features.	- n=4 diagnosed by NBS, n=3 with disease onset prior to diagnosis. - clinical features in screened patients: global developmental delay (3), seizures (2), dystonia (2), truncal hypotonia (1), macrocephaly (1). - clinical features in unscreened patients: macrocephaly in 2/3, and all the other symptoms mentioned above in all patients. - onset of symptoms after infection (4) or vaccination (1). - high excretion of organic acids in urine in all patients. - all patients had striatal and extrastriatal abnormalities in neuroimaging.		Indirectness (population differences) Imprecision (Small sample size)	3	Diagnostik
Mahajan et al. (2018) Indian Pediatr; 55(8):707	AEFI Surveillance – The Learning Curve Continues	Case report	n=1: 3M female patient	Adverse Events Following Immunization	2d after second dose of pentavalent vaccine, fever + 3 episodes of generalized tonic clonic seizures, each 1 minute. Normal examination. US: prominent lateral + third ventricles. Treatment: phenobarbitoine, seizure-free during hospital stay of 4 days. 4d later: lethargic and then apneic state leading to cardiac arrest and death. MRI: prominent extra-axial CSF spaces in frontotemporal region, cerebral convexities with widened sylvian fissures bilaterally + uniform thinning of corpus callosum → highly suggestive of GA1.	No NBS patient → "classic" course of unknown GA1	N=1 Indirectness (population differences)	3	Therapie
Märtner et al. (2021) J Inherit Metab Dis; 44(3):629-638	Impact of interventional and non-interventional variables on anthropometric long-term development in glutaric aciduria type 1: A national prospective multi-centre study	Prospective multicentre observational trial	n=79 diagnosed through NBS	Anthropometric long-term development (body weight, body length, body mass index [BMI], head circumference) Neurologic outcome (movement disorder, dystonia)	n=79 patients (=92% of patients identified by NBS between 2004 and 07/2016). - Mean age at last visit 8.77Y (cumulative follow up time 663Y) - 59 high excreter; 18 low excreter; 2 unknown. - Adherence to maintenance treatment: n=62; deviations: n=17. - Adherence to emergency treatment: n=70; deviations: n=9. - Neurologic outcome: n=53 asymptomatic; n=20 dystonia; n=1 ataxia; n=5 minor neurologic abnormalities.			2++	Monitoring

					- Non-adherence to emergency treatment → negative impact on body weight (mean SDS −1.07; *P* = .023) and body length (mean SDS −1.34; *P* = −.016) - Adherence to maintenance treatment allowed normal anthropometric development (SDS 0.01) - Non-adherence to MT → no direct negative impact on anthropometric development (in individuals without dystonia) - Longitudinal analysis: negative influence of severe dystonia on weight and length development over time (*P* < .001) - Supervision by a metabolic centre: Had no significant effect on anthropometric development. - Macrocephaly: more often found in female (mean SDS 0.56) than in male patients (mean SDS −0.20; *P* = .049), and also in individuals with high excreter phenotype (mean SDS 0.44) compared to low excreter patients (mean SDS −0.68; *P* = .016).				
Märtner et al. (2021) Sci Rep 11:20618	The biochemical subtype is a risk factor for cognitive impairment in glutaric aciduria type 1– a national prospective follow-up study	Prospective, observational, multi-centre study	107 patients diagnosed with GA1 in Germany between January 1999 and February 2020. 98 were correctly identified by NBS, 6 patients were missed by NBS and three maternal	Clinical outcome: motor symptoms or signs of MD Cognitive/intellectual and developmental outcome	Clinical outcome: All NBS patients did not show motor symptoms or signs of MD at diagnosis. At last visit, 43/72 patients (60%) did not show any motor symptoms, n=7 patients (10%) showed minor neurologic abnormalities and n=22 patients (31%) had MD, mostly dystonia (21/22) which was mild in n=11 patients (52%), moderate (n=8; 38%) or severe (n=2; 10%). Cognitive/intellectual and developmental outcome: Denver Developmental Screening Test (DDST): 15 patients (63%) showed normal development in all domains, 9 patients (27%, seven of whom had dystonic MD) showed isolated (n=3), combined (n=4) or global (n=2) developmental delay Bayley Scales of Infant Development (BSID) II or III: available for 19 patients with a median test age of 2.3 years (SD 0.9 years). Mean developmental quotient (DQ) was in the lower average range (91; SD 18) and stable over age (p=0.6883) but differed		Study limitations: different IQ-tests and adaptations of standard values. Possible difficulties in assessing very young patients. Limited number of tested patients with severe motor disabilities.	2++	Monitoring

			patients were identified due to positive NBS results of their unaffected children. Two biochemical subtypes were defined, i.e., high excreting (HE) and low excreting (LE) depending on the urinary concentration of GA.		between HE (n=14; mean DQ 86; SD 18) and LE patients (n=5; mean DQ 106; SD 8; p=0.0174). IQ-Tests: Patients aged three years up to adulthood were tested with IQ tests [HAWIVA-III, WPPSI-III/-IV; HAWIK-IV, WISC-IV/-V, WAIS-IV, K-ABC/K-ABC-II, SON-R 2.5-7: Mean age at last IQ test was 10.5 years (SD 4.6 years), mean IQ for all patients was 87 (SD 15). Cognitive performance in all patients was stable over time in the cross sectional (p=0.89) as well as longitudinal analysis (p=0.36). The biochemical subtype had a strong impact on full scale IQ with LE patients (mean IQ 96; SD 14) showing superior results compared to HE patients at last visit (mean IQ 84; SD 14; p=0.0164) Cognitive factors according to the Cattel-Horn-Carroll theory: 28 patients with an IQ-test and complete datasets with results for full scale and all five subscales. Mean IQ results from 91 for crystallized intelligence (SD 13) to 94 in fluid intelligence (SD 17) indicated homogenous performance on both subscale and full-scale IQ levels (mean IQ of this subset 89; SD 15; Fig. 6).				
Matsumoto et al. (2018) Pediatr Int; 60(1):67-69	Renal insufficiency mimicking glutaric acidemia type 1 on newborn screening	Case report	n=1		Patient with elevated C5DC in NBS, persisting for at least 4M, without the confirmation of GA1. - Failure to thrive. - Elevated serum creatinine, low eGFR (24 mL/min/1.73 m2), metabolic acidosis with normal anion gap, renal tubular damage with increased N-acetyl-beta-D-glucosaminidase (NAG; 6.1 U/L; reference range, 0–5.7) and b2-microglobulin (b2MG; 26 561 lg/L; reference range, 0–289), indicating renal insufficiency.	Detection bias (small sample size)	N=1 Indirectness (population difference)	3	Diagnostik

					- Diagnostic abdominal US: bilateral renal hypoplasia. Longitudinal dimensions: 39.0 mm and 39.7 mm (reference dimensions: 50.0 ± 5.5 mm). - At age 4M: C5DC remained high (0.29 nmol/mL; cut-off, 0.25), laboratory evaluations indicating dehydration due to renal insufficiency. - At age 6M: 8806H formula (Meiji, Tokyo, Japan) was given for renal insufficiency. - Renal dysfunction persisted until at least age 2;6Y (eGFR 39.4-45.1 mL/min/1.73 m2).				
Mehta et al. (2018) Anesth Essays Res; 12(2):601-603	Anesthetic Management for Fracture Head of Radius in a Child with Glutaric Aciduria type-1	Case report	n=1: 10Y male patient diagnosed by selective screening at age 2M after EC.	Anesthetic management	- Closed reduction of fracture head of radius under sedation. - Home medication: L-carnitine 500 mg (OD), riboflavin 60 mg (OD), pyridoxine. - Preoperative physical, airway, laboratory examination: normal. - Patient was kept nil per oral 4 h before the procedure when an i.v. infusion of 5% dextrose was started at 70 ml/h. - Preoperative blood sugar on the morning of surgery: 88 mg/dl, room air oxygen saturation: 99%. - Premedication with injection ondansetron 0.1 mg/kg. - Routine monitoring, induction with propofol 120 mg, fentanyl 30 µg - Use of Proseal laryngeal mask airway (LMA) size 2.5 was. - Maintenance of anesthesia with oxygen, nitrous oxide (33:66), sevoflurane. - Neuromuscular blockade with rocuronium 15 mg loading dose. - Analgesia: Injection diclofenac 50 mg. - Patient remained hemodynamically stable during the surgery which lasted 2 h, and in postoperative period. - Episode of hypoglycemia with blood sugar of 68 mg% 3 h postoperatively without clinical manifestations, managed with 10 ml of dextrose 25%.		Small sample size	3	Therapie

					- Oral feeding resumed 4 h after surgery, discharge after 36 h.				
Mhanni et al (2020) MGM Reports 2020; 25:100666.	Outcome of the Glutaric aciduria type 1 (GA1) newborn screening program in Manitoba: 1980 - 2020	Retrospective single-center study	n=40	Clinical outcome Treatment	Cohort 1 (n=20, diagnosed between 1980-2000): treatment with low-protein diet + carnitine + intermittent emergency treatment. Cohort 2 (n=19, diagnosed between 2000-2020): treatment with low-lysine diet + carnitine + intermittent emergency treatment. Acute encephalopathic crisis: 90 % (Cohort 1) vs. 60% (Cohort 2); Odds ratio 0.19 (0.02-1.2; p=0.06) Insidious onset of dystonia: n=2 (Cohort 1) vs. n=3 (Cohort 2). Asymptomatic: n=0 (Cohort1) vs. n=4 (Cohort 2).		Indirectness (population differences) Imprecision (small sample size)	2-	Treatment Monitoring
Mohamed et al. (2020) Saudi Med J. 2020 Jul;41(7):703-708	Incidence of newborn screening disorders among 56632 infants in Central Saudi Arabia. A 6-year study	Retrospective single-center study	n=56.632 infants, of which n=38 had 1/17 NBS disorders (n=3 with GA1) between 01/2012 and 12/2017.	Epidemiology of diseases detected through NBS	- n=3 patients with GA1 (incidence: 1:18.877).		Indirectness (population differences) Imprecision (small sample size)	3	Diagnostik
Mohammad et al. (2020) Brain Communications; 2(2):fcaa178	Magnetic resonance imaging pattern recognition in childhood bilateral basal ganglia disorders	Retrospective study	N=305 MRI scans of 201 children with 34 different disorders	MRI pattern recognition	Cluster 1: lesions dominantly affecting the striatum (glutaric aciduria type 1, propionic acidaemia, 3-methylglutaconic aciduria with deafness, encephalopathy and Leigh-like syndrome and thiamine responsive basal ganglia disease associated with SLC19A3)		Indirectness (population differences)	2-	Diagnostik Monitoring
Monbaliu et al. (2017) Lancet Neurol	Clinical presentation and management of dyskinetic cerebral palsy	Review			Oral or intrathecal baclofen are preferred (evt tip at cervical spine)			3	
Mosaeilhy et al. (2017) Metab Brain	Genotype-phenotype correlation in 18	Case series	n=18	Clinical outcome Mutation analysis	<u>n=18 patients</u> - consanguinity in 100%, similarly affected family members in 55,6%.		Indirectness (population differences)	2-	Diagnostik

Dis; 32(5):1417-1426	Egyptian patients with glutaric acidemia type I				- macrocephaly in 50%. - n=10 patients with acute onset, n=8 patients with insidious onset (of which n=4 developed acute crisis). - n=16 patients with developmental delay, dystonia in 75%. - n=14 HE, n=2 LE, n=2 unknown. <u>Mutation analysis:</u> - 14 mutations, of which 9 missense, 3 in 3'-UTR-Region, 1 nonsense, 1 silent. - 4 novel mutations (c.148T>A, c.158C>A, c.1284C>G, c.1189G>T). - c.*165A>G in 18/36 alleles, c.1204C>T in 13/36 alleles.		Imprecision (small sample size)		
Moseilhy et al. (2017) Metab Brain Dis; 32(1):35-40	Severe neurological manifestations in an Egyptian patient with a novel frameshift mutation in the Glutaryl-CoA dehydrogenase gene	Case report	n=1	Mutation analysis Clinical outcome Genotype-phenotype-correlation	Male patient, born from a first cousin consanguineous marriage. At 11M: <3rd percentile for body weight, 5th percentile for head circumference, generalized hypertonia + hyperreflexia, positive Babinski sign, intact superficial sensation, no cerebellar manifestation, mental + developmental dely, lack of head support. No dystonia, no convulsions. <u>Diagnostic:</u> - MS/MS, GC/MS: elevation of C5DC in DBS, GA (>58.400 mmol/mol creatinine) + 3OHGA (120 mmol/mol creatinine) in urine. - Brain imaging (MRI): frontotemporal hypoplasia, multiple abnormal white + gray matter structures such as caudate nucleus + putamen. <u>Mutation analysis:</u> novel homozygous frameshift mutation (c.644_645insCTCG, p.Pro217Leufs*14). <u>Treatment:</u> riboflavin, carnitine, controlled lysine + tryptophan diet regimen. At 1Y: severe dystonia. At 2Y: death after encephalopathic crisis during acute infection. → Possible correlation of genotype with severe phenotype?!		N=1 Indirectness (population differences)	3	Diagnostik

Ntorkou et al. (2021) Am J Neuroradiol; 42:1722-1726	Enlargement of the Optic Chiasm: A Novel Imaging Finding in Glutaric Aciduria Type 1	retrospective study	n=10	Neuroimaging	enlargement of the optic chiasm associated with signal abnormalities in the anterior intracranial visual structures observed in 6 of 10 patients., regardless of a previous metabolic crisis		Indirectness (population differences) Small sample size	2-	Monitoring
Numata-Uematsu et al. (2017) Brain Dev; 39(6):532-535	Reversible brain atrophy in glutaric aciduria type 1	Case report	n=1 female diagnosed by NBS	Brain MRI Motor development (Head control, sitting, walking) Mental development (not specified) Concentrations of C5DC, lysin, tryptophan	- Motor development: Good head control at 4M, independent sitting at 8M, walking alone at 14M. Normal motor and mental development at 26M. - Brain MRI at age 4M: widened operculum with dilatation of subarachnoid spaces surrounding atrophic bilateral frontotemporal lobes. - Brain MRI at 17M + 26M: atrophic lesion had disappeared. - No metabolic decompensation episode reported, normal development. → Early dietary modifications with lower level of glutarylcarnitine + administration of carnitine can lead to normal development.	Publication bias due to journals favoring positive outcome findings? Findings from case reports cannot be generalized.	Case study (N = 1) Authors don`t specify how the "normal" mental and motor development was conducted, no tests or scores are cited.	3	Monitoring
Patel et al. (2018) JIMD Rep; 40:85-90	Early Diagnosed and Treated Glutaric Acidemia Type 1 Female Presenting with Subependymal Nodules in Adulthood	Case report	n=1	Neuroimaging in adulthood	Female patient with macrocephaly + megalencephaly leading to the suspicion of GA1. Diagnosis (biochemical + enzyme activity) at age 2M before the onset of symptoms. MT: low protein diet + carnitine + riboflavin. No metabolic crises as a child, normal neurological presentation, but learning difficulties in school. Headache at age 12Y: diagnosed as being migrainous + related to idiopathic intracranial hypertension. 2 successful pregnancies at age 23 + 25Y. At age 28Y: presentation after 3 weeks of slurred speech + left facial weakness + numbness. MRI at age 22/26/28Y: callosal + periventricular white matter changes, age discordant parenchymal atrophy, multifocal subependymal nodules in lateral ventricles. Genetic testing for tuberous sclerosis negative, confirmation of GA1 via mutation analysis. ➔ subependymal nodules as natural progression of GA1 despite early diagnosis and metabolic control = surrogate of chronic neurotoxicity.		N=1 No detailed information about treatment, First MRI not clearly described (postnatal?, no „nodules" described)	3	Monitoring

Peake (2016) Clin Chem; 62(8):1159-1160	Seizures, Dystonia, and Spasms in a 14-Year-Old Child	Case report	n=1	Clinical outcome of late-diagnosed patient Biochemical analysis Mutation analysis	14Y male patient Medical history: basal ganglia stroke in infancy, hypoxic brain injury, dystonia, spasms. Treatment: Levetiracetam for seizure control. GC/MS: GA in urine 400 mmol/mol creatinine. Mutation analysis: homozygous c.1204C>T.			3	Diagnostik
Peng et al. (2018) Taiwan J Obstet Gynecol; 57(1):137-140.	Prenatal diagnosis of fetal glutaric aciduria type 1 with rare compound heterozygous mutations in GCDH gene	Case report	n=1	Prenatal diagnosis	22Y female, Gravida 4, Para 2 - First child: healthy - Second child: diagnosed with GA1 by NBS - Prenatal examination at 13-19 weeks of gestational age: Maternal IVS3+1G>A, paternal c.1240G>A. - Termination of pregnancy.		Indirectness (population differences)	3	Diagnostik
Peng et al. (2020) Int J Neonatal Screen; 6(1):16	Reducing False-Positive Results in Newborn Screening Using Machine Learning		n=2777 screen-positive babies (of which n=2542 false-positive).	False-positive results in NBS for four metabolic diseases: GA1, MMA, OTCD, VLCADD	Aim: Random Forest machine learning classifier on screening data to improve prediction of true and false positives. Data included 39 metabolic analytes detected by MS/MS + clinical variables such as gestational age and birth weight of n=2777 screen-positive babies (of which n=2542 false-positive) fpr GA1, MMA, OTCD, VLACDD. Results: Without changing the sensitivity to detect these disorders in screening, Random Forest-based analysis of all metabolites reduced the number of false positives for GA-1 by 89% (48 confirmed positive vs. 1344 First-Tier NBS false-positive vs. 150 Second-Tier (this study) false-positive). - Random Forest's ability to classify GA-1 false positives was found similar to results obtained using Clinical Laboratory Integrated Reports (CLIR). - Development of an online Random Forest tool for interpretive analysis of increasingly complex data from newborn screening.		Indirectness (population differences)	3	Diagnostik
Peng et al. (2020) J Inherit Metab Dis; 10.1002/jimd.12236	Ethnic variability in newborn metabolic screening markers	Retrospective study	n=100.000 screen-negative babies + n=2767 screen-	False-positive results in NBS for four metabolic diseases: GA1, MMA, OTCD, VLCADD	Analysis of screen-negative babies (n = 100 000) (blood metabolic markers measured by MS/MS and ethnicity status reported by the parents). Comparison of metabolic marker levels between major ethnic groups (Asian, Black, Hispanic, White) using		Indirectness (population differences)	2+	Diagnostik

	associated with false-positive outcomes		positive babies (of which n=2532 false-positive)		effect size analysis, which controlled for group size differences and influence from clinical variables. Correlation of marker level differences found between ethnic groups to NBS data from 2532 false-positive cases for four metabolic diseases: GA1, MMA, OTCD, VLCADD. 79% of the metabolic markers (34 of 43) had ethnicity-related differences. Black infants had elevated GA1 markers (C5DC, Cohen's d = .37, P < .001), and also higher false-positive rates for GA1.				
Piercy et al. (2019) BMC Pediatr; 19(1):349	What are the information needs of parents caring for a child with Glutaric aciduria type 1?	Qualitative study design, focus group with five parents (4 mothers and 1 fahther) of four children with GA1, one focus group discussion	Focus group with five parents of four children with GA1 (17y, 8y, 3y, 2y) - older children had been diagnosed clinically, younger children diagnosed through NBS	Gain insight into the information that parents needed and the ways in which they accessed and used information to manage their child`s condition.	Two themes were identified: "understanding the condition" and "managing the condition" **understanding the condition**: parent`s need to understand the scientific complexity of the condition and be aware of the worst scene scenario associated with the loss of metabolic control.  **managing the condition**: how parents coordinate and control the involvement of other carers and parents`need to be active partners in in medical managements.	Selection bias: Recruitment process of the parents: parents of children with GA1 from a regional metabolic center and via a national parents' metabolic support organization. Parents were approached by their clinician or by an organizer of the support group.	Study limitations: small group (n = 5) with children diagnosed by two different ways. No demographic information about the families collected. Only one focus group conducted	3	Monitoring
Pode-Shakked et al. (2014) Molecular genetics and metabolism reports 1:170-175	Glutaric Aciduria type I and acute renal failure — Coincidence or causality?	Case report	N=1 (6 years)	severe acute renal failure requiring dialysis	severe acute renal failure following a diarrheal illness and an initial suspicion of hemolytic uremic syndrome (HUS).		N=1	3	Monitoring

Pöge et al. (1997) Acta paediatrica 86:1144-1147	Early clinical manifestation of glutaric aciduria type I and nephrotic syndrome during the first months of life	Case report	N=1 Diagnosis: 10 weeks	Seizures (3 weeks), nephrotic syndrome (12 Weeks), death (22 weeks) due to end-stage renal failure	Nephrotic syndrome Renal histology: glomerular disorder with shrinking of glomerular tufts, increase in mesangial matrix, proliferation of extracapillary epithelial cells and formation of larger epithelial crescents. end-stage renal failure.		N=1	3	Monitoring
Pokora et al. (2018) Metab Brain Dis; 34(2):641-649	Mild phenotype of glutaric aciduria type 1 in polish patients – novel data from a group of 13 cases	Case series	n=13 patients of which n=3 diagnosed by NBS (Group 1), n=8 diagnosed by selective screening after the onset of symptoms (Group 2), n=2 diagnosed by high risk screening due to positive family history (Group 3)	Clinical outcome Biochemical parameters Mutation analysis Neuroimaging	- Group 1: all patients asymptomatic. - Group 2: diagnosis due to rapid increase of head circumference, enlarging fontanels, suggestive anomalies in brain imaging, delayed motor development. 1 patient developed EC, further normal motor development. - Group 3: 1 patient with vertigo + vomiting, 1 patient asymptomatic. - Other symptoms: speech delay/deficits or poor language ability (4/13), learning difficulties (2/13), mild intellectual disability (2/13). - GC/MS: 5 LE, 8 HE. - Mutation analysis: c.1204C>T (p.Arg402Trp) most frequent (13/25 mutated alleles) - Neuroimaging: Characteristic findings for GA1 as described before.		Imprecision (classification of patients), definition of biochemical subtype	2-	Diagnostik
Qian et al. (2016) World J Pediatr; 12(3):368-371.	Recurrent rhabdomyolysis and glutaric aciduria type I: a case report and literature review	Case report (reported patient N = 1) and literature review	Report of a child with recurrent rhabdomyolysis and undiagnos	Recurrent rhabdomyolysis Mutation analysis	4,5Y female patient with recurrent rhabdomyolysis 1.) 2,5Y high fever, 2d fatigue, paleness, convulsion, muscle strength 4/5; diagnosis of rhabdomyolysis, treatment with fluid supplementation + urine alkalization for 3d. 2.) 3,5Y shortness of breath + fatigue for 3d, muscle strength 2-3/5, muscle biopsy: decreased	Study design: retrospectively, may not contain all relevant data.	Case report (N =1). No detailed information on how the “normal development”	3	Monitoring

		(reported patients N =3).	ed GA1 (own patient) and three patients with rhabdomyolysis and GA-1 discovered by literature review.		muscle fiber density; diagnosis of rhabdomyolysis and treatment as before. 3.) 4,5Y mild respiratory distress + muscle strength 2/5. Metabolic diagnostic: MS/MS, GC/MS leading to suspicion of GA1, mutation analysis revealing homozygous missense mutation c.764C>T. Start of low protein diet + amino acid / protein supplement + carnitine. Literature: 3 more patients with rhabdomyolysis caused by viral infection or febrile illness. Fever in all patients, also common: encephalopathy, shock, myoglobinuria, respiratory distress → 2 died, 1 disabled. → altered bioenergetics due to the metabolic disorder as potential precipitating factor for rhabdomyolysis	Information bias, subjectivity of the reporter. Publication bias due to journals favoring positive-outcome findings? Findings from case reports cannot be generalized.	was analysed provided.		
Rahda Rama Devi et al. (2016) Brain Dev; 38(1):54-60	Spectrum of mutations in Glutaryl-CoA dehydrogenase gene in glutaric aciduria type I – Study from South India	Case series	n=12 patients of which n=11 diagnosed in infancy / childhood, n=1 diagnosed in newborn period.	Genetics neurology	- In total, n=11 mutations (n=9 homozygous, n=1 heterozygous, n=2 synonymous mutations). - 4 novel mutations (p.Q162R, p.P286S, p.W225X, p.V410M). - Milder clinical presentation if patients are heterozygous or have a benign synonymous SNP.		Indirectness (population differences) Imprecision (small sample size)	2-	Diagnostik
Rajani et al. (2018) J Clin Imaging Sci; 8:50	A Case of Mistaken Identity: Glutaric Aciduria Type I Masquerading as Postmeningitic Hydrocephalus	Case report	n=1	Neuroimaging	- 8Y male, consanguineous parents, 6th of seven children (the youngest suffering from similar problems). - Progressive cranial enlargement since birth. - Normal milestones till age 6M. - Regression of milestones after acute episode of meningitis at age 6M. - Exam: Macrocrania, severe muscular hypotonia with superimposed dystonic movements. - Diagnosis: Postmeningitis hydrocephalus		Indirectness (population differences) Imprecision (small sample size, only one patient)	3	Diagnostik

					- MRI at age 7Y: characteristic findings for GA1, leading to this diagnosis.				
Rayat et al. (2021) Clin Case Rep; 9:e04749	A novel mutation in the glutaryl-CoA dehydrogenase gene (GCDH) in an Iranian patient affected with Glutaric acidemia type 1	Case report	n=1	Mutation analysis	Mutation c.536T>C (p. Leu179Pro) in GCDH gene, has not been reported so far, but the in-silico analysis and clinical symptoms of the patient indicated that the mutation is pathogenic full stop		Indirectness (population differences)	3	Diagnostik
Sanju et al. (2021) J Pediatr Intesive Care; 10:65-70	Glutaric Aciduria Type 1: A Case Report and Review of Literature	Case report	n=1	Neuroradiologic imaging	8M male - referred with history of fever, convulsions, dystonic posturing, altered sensorium, loss of motor and mental milestones since 1M - MRI brain: frontoparietal atrophy, “bat-wing appearance,”, basal ganglia changes - Carnitine + acylcarnitine profile: low total carnitine, very low free carnitine, and low free/acylcarnitine ratio, normal levels of plasma amino acids. - Urine gas chromatography mass spectrometry: elevated level of ketones (3-hydroxybutyric acid and acetoacetate) and glutaric acid with the presence of 3-hydroxyglutaric acid. - Diet modification and pharmacotherapy with riboflavin and carnitine arrested the neurological deterioration in the patient.		Indirectness (population differences) Imprecision (small sample size, only one patient)	3	Diagnostik
Sarangi et al. (2017) J Pediatr Neurosci; 12(1):85-86	Glutaric Aciduria Type I: A Rare Metabolic Disorder Mimicking as Choreoathetoid Cerebral Palsy	Case report	n=1	Neuroradiologic imaging Biochemical analysis	7Y male - Choreoathetoid movements of upper & lower limbs, dystonia, slurring of speech since age 1;6Y - Born after uncomplicated pregnancy, no consanguinity, no history of birth asphyxia or jaundice during infancy. - History of generalized tonic– clonic convulsion following febrile illness at age 1;6Y - Involuntary movements started following the episode of seizure. - <u>Exam</u>: head circumference: 58 cm (>97th centile, macrocephaly), conscious, well oriented, dysarthria, hypotonia in both upper + lower limbs,		Indirectness (population differences) Imprecision (small sample size, only one patient)	3	Diagnostik

					diminished reflexes, generalized choreoathetosis, dystonia of both upper + lower limbs. MRI (Axial T2-weighted): bilateral frontotemporal atrophy, wide Sylvian fissure ("bat-wings") - Confirmation of GA1 through MS/MS + GC/MS. - Treatment: Riboflavin, carnitine, protein-restricted low-lysine/ low-tryptophan diet - Follow-up after 3M: some reduction in involuntary movements.				
Schillaci et al. (2016) Mol Genet Metab; 119(1-2):50-56	The M405V allele of the glutaryl-CoA dehydrogenase gene is an important marker for glutaric aciduria type I (GA-I) low excretors	Case report + case series	n=9 LE patients + n=5 HE patients (+1 GA2 patient)	Mutation analysis Biochemical analysis including urinary C5DC Clinical outcome	Patient 1: first evaluation at 1Y due to developmental delay, failure to thrive, dystonic posturing, hypotonia, brain MRI showing basal ganglia changes. Mutation analysis: M405V, V133L (novel). Patient 2: acute onset of symptoms at 5,5M with left sided hemiparesis with spasticity during inter-current illness. Brain MRI: increased signal bilaterally in basal ganglia. Mutation analysis: M405V, V400M. Treatment: low-protein diet, riboflavin, carnitine. Severe MD at age 11Y. Patient 1-9: compound-heterozygous for M405V with GCDH activity of 4-25%. - 3 patients screened by NBS, of which 1 patients was missed by NBs - 6 patients not screened by NBS developed acute striatal necrosis within the first year of life. Patient 1-15 (10-15 = 5 HE + 1 GA2): linear relationship between plasma C5DC + urinary C5DC → urinary C5DC as a specific marker for GA1, especially for patients with normal urine organic acids + plasma acylcarnitine profiles.		Small sample size	2-	Diagnostik
Schmidt et al. (2020) J Inherit Metab Dis; 10.1002/jimd.12233	Impact of enteral arginine supplementation on lysine metabolism in humans: A proof-of-concept for lysine-related inborn errors of metabolism	Proof of concept study Measurement of oxydation of a stable isotope tracer L-(1.13C)lysi	n=5 healthy men (age 22-25 years)	Impact of enteral arginine supplementation on lysine metabolism, lysine oxidatio and lysine plasma concentrations	- Increasing doses of L-arginine Hydrochloride caused a linear decrease in whole-body lysine oxidation. Plasma arginine concentration increased, plasma lysine concentration decreased below normal range with high arginine intakes. - Results suggest 300-600 mg/kg/d of L-arginine Hydroxychloride + lysine intake restricted to DRI is needed to reduce enteral lysine uptake + systemic lysine oxidation. Whole-body lysine oxidation and plasma lysine concentrations decreased	Age, Gender only effect on plasma amino acid examined, not on CSF levels and/or lysine influx across BBB	Only healthy individuals, no patients	3	Therapie

		ne to 13 CO_2 in response to ingestion of a single oral administration of arginine (50-600 mg/kg/d)			significantly with increasing dosage of oral arginine intake. Approx. 300-600 mg/kg/d of oral arginine are needed to reduce systemic lysine oxidation	Selection bias (only 1 group)			
Serrano Russi et al. (2018) Mol Genet Metab; 125(3):276-280	Malignant brain tumors in patients with glutaric aciduria type I	Cases series	n=3 patients, n=1 diagnosed by NBS (poor compliance to prescribed treatment), n=2 diagnosed in symptomatic state	Malignant brain tumors	Patient 1: female patient, consanguineous parents, diagnosed with GA1 through NBS, treatment with carnitine + moderately reduced protein diet (1,5-2/g/kg/day), poor compliance. - no neurological symptoms until 6;4Y: partial 6th cranial nerve palsy + vomiting. - MRI: mass on the roof of the 4th ventricle centered in inferior medullary vellum, resulting in hydrocephalus. → medulloblastoma (WHO grade IV) - Surgical resection + ET, spinal irradiation + CHT. - Post-OP: impairment + amblyopia of left eye, fine + gross motor deficits. - 10Y: growth parameters + neurological examination completely normal. Patient 2: male Patient, diagnosed "clinically" (macrocephaly?) at 1M - Mutation analysis: compound heterozygous for c.641C>T, c.1204C>T. - Treatment: protein restricted diet, levo-carnitine, ET. - MRI at 9Y: prominence of bilateral subarachnoid space in sylvian fissure + anterior middle cranial fossa with bilateral + symmetric increase in T2 in the centrum semiovale, no diffusion abnormality. Subependymal nodule in left lateral ventricle. MRI at 14Y (no neurological deficits): cerebellar mass measuring 4,1x3,2x2,4 cm		Small sample size Population differences	3	Monitoring

					→ nodular/desmoplastic variant medulloblastoma, WHO grade IV. - Surgical resection + RCHT. - 15;8Y: some residual neurological deficit, no dystonia. <u>Patient 3:</u> 2Y male patient - bilateral temporal + frontal subdural hematoma, diagnostic workup → GA1. - <u>Treatment</u>: low protein diet, amino acid supplementation, carnitine, riboflavin. - <u>Progressive extrapyramidal symptoms</u> (dystonia + facial dyskinesia) with aggravation after febrile episode + metabolic decompensation at 8Y <u>-MRI:</u> white matter abnormalities, bilateral thalami involvement. <u>- 23Y:</u> sudden episodes of vomiting + lethargy. <u>- Brain CT:</u> intraparenchymal hemorrhage in right basal ganglia within neoplastic lesion. → glioblastoma WHO grade IV. - Full cycle of CHT with temozolomide, tumor relapsed. - 24Y: death. <u>Pathophysiological hypotheses:</u> <u>- GA:</u> 1) impairment of Krebs cycle with subsequent increase of glycolytic flux; 2) impairment of glutaminolysis with increased availability of glutamine for cancer cells. <u>- 3OHGA</u> unclear: possible tumorigenic properties vs. protective effects against tumorgenesis. → MRI for monitoring and early detection of malignant brain tumors in GA1				
Shadmehri et al. (2019) J Cell Biochem; 120(3):3367-3372	Molecular genetic study of glutaric aciduria, type I: Identification of a novel mutation	Case report	n=1 patient, diagnosed with GA1 by selective screening	Mutation analysis	- Novel mutation: c.1174C>A, p.Arg383Ser (missense mutation)		Indirectness (population differences)	3	Diagnostik

Shaik et al. (2020) Meta Gene https://doi.org/10.1016/j.mgene.2020.100804	Molecular identification of glutaryl CoA dehydrogenase gene variations and clinical course in three glutaric aciduria type I patients	Case series	n=3	Mutation analysis Neuroimaging Clinical outcome	1) 9M boy, consanguineous parents, no family history of GA1/metabolic dieseases. - Presented with motor regression. - Head circumference 48 cm (no macrocephaly) - Elevated C5DC (1.3 µmol/l), GA (26 mmol/mol creatinine), 3OHGA (33 mmol/mol creatinine) - CT: prominence of the ventricular system, bilateral frontotemporal atrophy with widening of adjacent CSF spaces, wide operculum demonstrating a characteristic "bat-wing“ - Mutation analysis: homozygous S189T (g.9893 G>C), likely pathogenic - Treatment with low-lysine diet, carnitine + riboflavin supplementation, emergency treatment, Backofen, gabapentin, risperidone. 2) 8M boy, consanguineous parents, elder sister had GA1, died at 3Y. - Delayed milestones + dystonia. - C5DC 1.7µmol/l. - CT: cerebral atrophy with expansion of CSF spaces anterior to the temporal lobes, dilation of the Sylvian fissures and widened operculam - Mutation analysis: homozygous R386P (g.11618G>C), likely pathogenic. - Treatment with low-lysine diet, carnitine + riboflavin supplementation, emergency treatment, Backofen, gabapentin, trihexyphenidyl. - Death of the baby 3) 5M girl, consanguineous parents. - Presented with seizures + delayed milestones. - C5DC 1.7µmol/l. - MRI: wide CSF spaces, dilatation of the Sylvian fissures, hyper intensities in the bilateral striatum, and in the caudate and putamen. - No macrocephaly. - Mutation analysis: homozygous W225S (g.10084G>C), likely pathogenic.	Consanguineousity	Imprecision (small sample size) Indirectness (population differences)	3	Diagnostik

					- Treatment with low-lysine diet, carnitine + riboflavin supplementation, emergency treatment, Backofen, gabapentin, trihexyphenidyl. - Weight gain was found in this patient.				
Sharawat et al. (2018) J Pediatr Neurosci; 13(3):349-351	Glutaric Aciduria Type 1 with Microcephaly: Masquerading as Spastic Cerebral Palsy	Case report	n=1	Neurology Anthropometrics Genetics MRI	- 13M boy - Normal antenatal period, APGAR 3 at 5 min, 6 at 10 min, no NBS performed. - Head circumference 33,8cm. - Developmental delay since early infancy. - Progressive spasticity since age 6M, diagnosis of cerebral palsy at 8M & start of treatment with baclofen & physiotherapy. - Acute viral illness at 12M → loss of all acquired milestones, development of intermittent twisting of limbs & arching of body. - Exam: body weight + length < fifth percentile, microcephaly (z-score <3), bilateral spasticity, hyperreflexia, generalized dystonia. - MRI: widened Sylvian fissure, hyperintensities in bilateral globus pallidus, bilateral frontoparietal atrophy along with white matter loss. - Mutation analysis: homozygous mutation in GCDH gene. - Treatment: Trihexyphenidyl, L -carnitine, high dose riboflavin (100mg/day), low-protein diet with lysine + tryptophan restriction.			3	Diagnostik
Sherazi et al. (2017) J Coll Physicians Surg Pak; 27(4):218-221	Selective Screening for Organic Acidurias and Amino Acidopathies in Pakistani Children		n=3 patients with GA1 diagnosed by selective screening	Incidence of GA1 (and other Organic Acidurias and Amino Acidopathies) in Pakistani Children	- n=3 patients with GA1 (of n=41 patients with Organic Acidurias, of n=1.866 screened patients).		Indirectness (population differences)	3	Diagnostik
Shibata et al. (2018) Mol Genet Metab Rep; 16:5-10	Diversity in the incidence and spectrum of organic acidemias, fatty acid oxidation disorders, and		n=44 patients with GA1 diagnosed by selective screening in Asian	Incidence of GA1 (and other IMDs) in Asian countries	- n=44 patients with GA1 diagnosed by selective screening in Asian countries (of 39.270 screened patients). - Incidence of GA1 in Japan: 1:280.000 - In Japan, GA1 was found in 10% of the cases with organic acidemias through NBS, but only in 3% of the cases using selective screening.		Indirectness (population differences)	2-	Diagnostik

	amino acid disorders in Asian countries: Selective screening vs. expanded newborn screening		countries, n= 12 patients with GA1 diagnosed by expanded NGS in Japan						
Shur et al. (2021) Pediatr Radiol; 51: 1029-1043	Genetic causes of fractures and subdural hematomas: fact versus fiction	Review		genetic testing in cases of suspected child physical abuse				2-	Monitoring
Simon et al. (2018) J Chromatogr B Analyt Technol Biomed Life Sci; 1097-1098:101-110	Quantitation of plasma and urine 3- hydroxyglutaric acid, after separation from 2-hydroxyglutaric acid and other compounds of similar ion transition, by liquid chromatography-tandem mass spectrometry for the confirmation of glutaric aciduria type 1	Methodology			→ LC-MS/MS method accurately quantified plasma + urine 3OHGA concentration after successful resolution from 2OHGA + other compounds with similar ion transitions. → Suitable method for confirmatory testing of 3OHGA, as follow-up to abnormal NBS result.		No clinical data	3	Diagnostik
Singh et al. **(**2020) Acad Emerg Med 27(9):832-843	The Effect of Patient Observation on Cranial Computed Tomography Rates in Children with Minor Head Trauma			CT Neurology	"Cranial CT use was significantly lower with planned observation (adjusted odds ratio [OR] = 0.2, 95% confidence interval [CI] = 0.1 to 0.1), with no difference in missed ciTBI [Clinically important traumatic brain injury] rates. " "**Conclusions:** Even in a setting with low overall cranial CT rates in children with minor head trauma, planned observation was associated with decreased cranial CT use. This strategy can be safely implemented on selected patients in the			2+	Monitoring

					PECARN intermediate- and higher-risk groups for ciTBI. "				
Sitta et al. (2021) Metab Brain Dis; 36:205-212	Clinical, biochemical and molecular findings of 24 Brazilian patients with glutaric acidemia type 1: 4 novel mutations in the GCDH gene	Retrospective study	n=24	clinical phenotype biochemical analysis molecular analysis	- all patients diagnosed by high levels of glutaric and/or 3-hydroxyglutaric and glutarylcarnitine; confirmation by genetic analysis. - Most patients had early-onset severe form with neurological deterioration, seizures and dystonia, usually following an episode of metabolic decompensation. - Despite early symptomatology, diagnosis took a long time for most patients. - 13 variants in GCDH gene, 4 of them were novel: c.91 + 5G > A, c.167T > G, c.257C > T, and c.10A > T. - most common mutations: c.1204C > T (p.R402W), c.91 + 5G > A (IVS1 ds G-A + 5) (new mutation)		Indirectness (population differences)	2-	Diagnostik
Sivamurukan et al. (2020) Indian J Pediatr; 87(6):484-485	Riga Fede Disease with Glutaric Aciduria Type 1	Case report	n=1 patient	Clinical endpoints	7M female patient with developmental regression + dystonia since age 3M. - Difficulty with breast feeding revealed loose natal mandibular central incisor along with linear ulcer over ventral surface of the tongue = Precocious riga fede disease. - Extraction of the teeth → healing of the ulcer → feeding without problems.		N=1 Indirectness (population differences)	3	Diagnostik
Smon et al. (2018) Clin Biochem; 52:48-55	Next generation sequencing as a follow-up test in an expanded newborn screening program	Pilot study of expanded newborn screening	n=10.048, of which n=85 were evaluated at a metabolic follow-up and n=80 of them were analyzed using NGS	Next-generation sequencing in expanded newborn screening program	<u>Study population:</u> n=10.048, of which n=85 were evaluated at a metabolic follow-up and n=80 of them were analyzed using NGS, n=1 diagnosed with GA1.		Only one patient with GA1	2+	Diagnostik
Spenger et al. (2021) Int J	Glutaric Aciduria Type I Missed by Newborn	Case series	n=4	Biochemical analysis Mutation analysis	four cases from three families - correctly performed NBS did not detect the condition.		Small sample size	3	Diagnostik

Neonatal Screen; 7:32	Screening: Report of Four Cases from Three Families				- Glutarylcarnitine concentrations were either normal (slightly below) or slightly above the cut-off. Ratios to other acylcarnitines were also not persistently elevated. → 3 cases defined as screen negative, 1 case defined as normal, after a normal control DBS sample. → 1 patient was diagnosed after an acute encephalopathic crisis, 3 patients had insidious onset of the disease. - GA-1 was genetically confirmed in all cases. ➔ Despite extensive efforts to increase sensitivity and specificity of NBS for GA-1, by adjusting cut-offs and introducing various ratios, the biological diversity still leads to false-negative NBS results for GA-1.				
Stepien et al. (2017) JIMD Rep; 41:29-36	Two Uneventful Pregnancies in a Woman with Glutaric Aciduria Type 1	Case report	n=1: 28Y female, diagnosed with GA1 at 11Y by family screening.	Pregnancies in a patient with GA1	<u>Pregnancy 1:</u> at age 23Y - adjustment of dietary treatment including "unwell day" plan - complications: pre-eclampsia with hypertension (highest BP 160/100 mmHg) + proteinuria (protein+) (third trimester); headache + complaints of flashing lights, resolved with labetalol 200 mg twice-daily in the last 6 weeks of pregnancy. - Emergency caesarean section, post-partum hemorrhage (need of 2 units of red cells). - "Unwell day" plan post-delivery for 5 days (reduced protein intake). - NBS of the baby initially positive, no abnormalities at d4. - Normal neurological exam 2M post-partum. <u>Pregnancy 2:</u> at age 27Y - adjustment of dietary treatment including "unwell day" plan - complicated by frequent gastrointestinal symptoms. - emergency caesarean section - NBS of the baby initially positive, no abnormalities at d4.		N=1	3	Monitoring
Strauss et al. (2020) Mol	Glutaric acidemia type 1: Treatment	Prospective	n=168	Mutation analysis Dietary treatment	<u>- Cohort I</u>: n=60 patients (DOB 2006-2019), diagnosis at age 0-14D (asymptomatic) through	Data for Cohort 1 were	Monocentric design	2+	Diagnostik

Genet Metab; 131:325-340	and outcome of 168 patients over three decades	observational study Cohort I, retrospective study Cohort II+III	Cohort I: n=60 Cohort II: n=57 Cohort III: n=51	Clinical outcome Medical + surgical management of dystonia Developmental and cognitive outcomes: - Developmental: During the first two years age (months) of achieved independent sitting, crawling, walking and speaking. - Cognitive: A subgroup of 10 children from Cohort 1 (median 7.0, range 5-12 years) completed Stanford-Binet-Intelligence Scales 5th Ed. With 8 subscales: full scale intelligence quotient (FSIQ), verbal IQ, non-verbal IQ, working memory and knowledge, visual-spatial, quantitative and fluid reasoning.	NBS (C5DC in dried blood spots / GCDH c.1262C>T from umbilical cord blood); consistent treatment with lysine-free, arginine-enriched formuala + L-carnitine + emergency treatment. - Cohort II: n= 57 patients (DOB 1989-2018), diagnosis through NBS, treatment with emergency treatment, low-protein diet (1-1.3 g/kg*d), NO lysine-free metabolic formula. - Cohort III: (DOB 1973-2019); diagnosis through workup for motor disability (90%) / incidentally through cascade testing. NO NBS, NO preventative therapies. Treatment + Monitoring (Cohort I) - Monitoring intervals: <1Y every month; <2Y every 2 months. - Dietary Therapy: L-carnitine supplementation 100 mg/kg/d up to age 2Y - Strict Lys-Arg+ diet was associated with median plasma lysine and arginine concentrations of 80 and 98 µmol/l. Normal concentrations of all SLC7A1/5 amino acid substrates, except lysine (38% below reference median) → estimated cerebral lysine uptake 40% lower than in controls / GA1 patients with unrestricted diet. - Dietary adherence: full adherence up to age 2Y, decreasing up to age 7Y (12% adherence) related to increasing plasma lysine concentration. - L-carnitine supplementation in 32% after age 6Y (decreasing plasma carnitine levels, no clinical signs of carnitine deficiency). CKD (Cohort I): No signs of renal insufficiency among patients ≤3 years of age (mean serum creatinine 0.27±0.06, range 0.20–0.40 mg/dL; over the last three decades, no GA1 patient with overt renal failure Psychomotor outcome: - Incidence of striatal degeneration 7%, 47%, 90% (Cohort I, II, III) - No neurologic injuries after age 19M. - Better functional outcome in patients with insidious onset than encephalopathic crisis.	collected prospectively, for Cohorts 2 and 3 retrospective interviews were conducted. "Control-group" which is used for comparison in developmental and cognitive testing in Cohort 1 consists of unaffected siblings – might be a selections bias, population differences (only families with at least one child With GA1). Detection bias (only one measurement) Selection bias (only one group included)	Majority of patients are homozygous for a single GCDH gene variant Cohorts I-III differ in age (Mean: 5.4, 14.8, and 21.8 years) Only a small group (N =10) from Cohort 1 conducted cognitive testing. No detailed information on cognitive testing procedure and detailed scores provided. Poor information about MRI results of patient (number, precise description of MRI changes missing)		Therapie Monitoring

					Dystonia: - Diazepam 3-4/d commonly used. - Baclofen (enteral) rarely. - Levodopa + trihexyphenidyl: ineffective against GA1-associated dystonia. - Continuous intrathecal (n=2) / intraventricular (n=2) baclofen allowed moderate relief. - DBS in 1 patient with subjective, but not objective improvement. - Orthopedic procedures in 16 patients (posterior spinal fusion, proximal femur varus detoriation osteotomy / pelvic osteotomy). Renal function: n=0 acute or chronic renal failure (but without routine testing) Anthropometric development (until age 2 years): Normal development with MT according to guideline Cognitive: 10 subjects from Cohort I who were old enough for cognitive testing (median 7.0, range 5–12 years) scored similar to their age-matched control siblings (median 8.9, range 6.0–17.1 years) on FSIQ and SB-5 subscales [verbal IQ (VIQ), non-verbal IQ (NVIQ), working memory (WM), and knowledge (K), as well as visual-spatial (VS), quantitative (QR) and fluid (FR)]. Neurorad. Imaging: Bilateral neuronal loss and gliosis of the lentiform nuclei (n=?) Cohort II+III: ca. 85% lesions acute onset with generalized dystonia Cohort I: ca. 50% with striatal degeneration present with insidious motor delay (?) Mortality: 91 w/o striatal degeneration are alive (mean, 9.6 years); while 14/59 (24%) with striatal lesions died from complications of dystonia				
Thomas et al. (2018) Metab Brain Dis; 33(2):537-544	Favourable outcome in a child with symptomatic	Case report	n=1 Male patient	Simultaneous occurrence of GA1 & HIV	HIV-infected South African male - Macrocephaly at birth - Combination antiretroviral therapy (ART) at 8 weeks	Findings from case reports cannot be generalized.	Case study (N =1)	3	Diagnostik

	diagnosis of Glutaric aciduria type 1 despite vertical HIV infection and minor head trauma	For the comparison of IQ and Purdue-Pegboard Scores means from literature of uninfected neighbourhood controls at the age of 9 years are provided.	with HIV, mother had HIV infection, which was detected during pregnancy	Neurodevelopment/Neuropsychology Fine motor, dexterity (Purdue Pegboard) Neuroimaging (CT and MRI) Neurological examinations	- Short-lived focal seizures at 16M, normal neurological examination - Neuroimaging: temporal lobe atrophy, subtle hyperintense signal change in globus pallidus, focal haemosiderosis in right Sylvian fissure region. Then diagnosed with GA1. Follow-up neuroimaging at 9 years showed no evidence of progressive atrophy. - Metabolic screening: GA in urine 96 mmol/mol creatine - Mutation analysis: Arg293Trp - Treatment: L-carnitine + low protein diet - Pulmonary tuberculosis at 21M, requiring 6 months treatment. no neurologic motor symptoms. - Neurodevelopmental test scores at 7 & 9Y below average, but at the same level as unaffected neighborhood controls, mild language delay at 3½ years. His scores on the Purdue pegboard test (at 9 years were above the average raw scores for unexposed uninfected control children.				Monitoring
Tsai et al. (2017) J Chin Med Assoc; 80(4):253-261	Experiences during newborn screening for glutaric aciduria type 1: Diagnosis, treatment, genotype, phenotype, and outcomes	Case series	n=9 patients diagnosed with GA1 by NBS (of 1.490.636 screened babies) + n=2 patients diagnosed clinically	Incidence of GA1 in Taiwan Carnitine loading test Mutation analysis Clinical outcome Cognitive functioning Neuroimaging	Incidence of GA1 in Taiwan: 1:106.474 Cases 1-5: NBS + recommended therapy (MT + ET) Case 6: NBS + late start of therapy, insidious onset GA1? Case 7-9: NBS + delayed ET Case 10+11: clinically diagnosed N=2 with pendular nystagmus (n=1 with vision impairment, bilateral optic atrophy and bil. central scotoma → complete ophthalmologic evaluation is suggested Carnitine loading test: significant elevation in C5DC concentrations after the test in all affected newborns, but not in false-positive newborns. Mutation analysis (n=10 patients): 2 novel mutations (c.106delCA, c.873C>A), most common mutation: IVS10-2A>C (12/20 alleles)		Indirectness (population differences) Small sample size Small groups (MRT)	2-	Diagnostik Therapie Monitoring

					Clinical outcome: Macrocephaly in 45% of all patients, EC in 22% (NBS group) vs. 100% (diagnosed clinically), pendular nystagmus in n=2 NBS patients (with optic atrophy in case 1 + T2 hyperintensity within the left occipital lobe in case 2). Dystonia in 22% (NBS group) vs. 100% (diagnosed clinically). Cognitive functioning: Significant differences between 3 groups (1: NBS + good compliance, 2: NBS + delayed ET, 3: diagnosed clinically). Neuroimaging: (1) infantile stage: widening of sylvian fissure. (2) 1-8 weeks after EC: T2 hyperintensity at putamen, caudate nucleus, globus pallidus, supratentorial white matter. DWI + ADC: restricted diffusion, mainly in globus pallidus + putamen. (3) Long-term follow-up after EC: T2 hyperintensities within supratentorial white matter, dilatedventricles + atrophy of putamen, caudate nucleus, globus pallidus. DWI+ ACD: restricted diffusion within affected supratentorial white matter + putamen. (4) Follow-up MRI of patients without EC: T2 hyperintensity + restricted diffusion within supratentorial white matter. T2 hyperintensity also within globus pallidus.				
Tuncel et al. (2018) J Inherit Metab Dis; 41(5):765-776	Organic acidurias in adults: late complications and management	Literature review		Clinical				4	Diagnostik Monitoring Therapie
Ukmanova et al. (2020) Mov Disord Clin Pract;	Inborn Errors of Metabolism in Adults: Two Patients with Movement	Case series	n=2 adult patients with GA1	Clinical phenotype Mutation analysis	1: 45Y female - progressive jerky movements of the limbs, gait disturbances, speech impairment.		Small sample size	3	Diagnostik

7(Suppl3): S85-S88	Disorders Caused by Glutaric Aciduria Type 1				- “clumsy child, slower in running than the others”, diagnosed with cerebral palsy 3Y because of movement abnormalities - older brother died after seizures with cerebral bleeding when he was 20 years old - Neurological examination: slight dysarthria, generalized chorea with possible additional myoclonus, and dystonia - Brain MRI: very mild, bilaterally symmetric gliosis in the dorsal putamen without significant atrophy. - Metabolic testing significantly elevated GA + 3OHGA in urine + glutarylcarnitine in DBS - DNA analysis: 2 pathogenic mutations in GCDH gene (compound heterozygous mutations: c.1148G > A [p.Arg383His] and c.1262C > T [p.Ala421Val]). - dietary treatment (low protein and high energy diet regimen and carnitine and riboflavin supplementation) was introduced. → Since the initiation of treatment 4 years ago, the patient has been stable without significant deterioration, and the diet is well-tolerated. 2: 45Y female - generalized involuntary movements that were more pronounced on the left side of her body. - mother noticed these involuntary movements from a very young age, slightly progressive over the years. - had several different diagnoses including cerebral palsy, functional movement disorder, and tics. - Pregnancy and birth were normal. - With the exception of delayed walking (at the age of 2 years), motor milestones were normally obtained. - Neurological examination: dystonia of the neck, mild orofacial dystonia, slight dysarthria. Eye movement examination: some saccadic intrusions during smooth pursuit. jerky, chaotic movements of the arms during rest, posture, and action, thought to be consistent with chorea and possible additional myoclonus.				

					- movements were more pronounced on the left side. There was dystonia of the hand during writing and tapping with intermittent abnormal posture of the feet - brain MRI: abnormalities of dorsal putamen - dystonia gene panel: 2 pathogenic mutations in GCDH gene (compound hetero- zygous mutations c.482G > A [p.Arg161Gln] + c.1262C > T [p.Ala421Val]), - No dietary treatment, but emergency treatment was advised during catabolic periods. - Since diagnosis 6 Y ago, only slight progression of MD				
Vargas et al. (2018) Arch Med Res; 49(3):205-212	Selective Screening of Fatty Acids Oxidation Defects and Organic Acidemias by Liquid Chromatography/ tandem Mass Spectrometry Acylcarnitine Analysis in Brazilian Patients		n=7.268 selectively screened individuals, of which n=14 with GA1	Biochemical analysis (LC/MS/MS) Clinical outcome Incidence of GA1	n=7.268 selectively screened individuals due to clinical symptoms, of which n=14 were diagnosed with GA1 - Mean age at diagnosis: 1.35Y (range 16D – 4.25Y) - Symptoms: Neurological regression (57%), convulsions (50%), neuropsychomotor delay (50%).		Indirectness (population differences)	2-	Diagnostik
Vester et al. (2016) Eur J Pediatr; 175:1001–1006	Occurrence of subdural hematomas in Dutch glutaric aciduria type 1 patients	Retrospective cohort study	n=25 patients with GA1 (=all registered GA1 patients in the Netherlands); n=17 diagnosed due to clinical symptoms / family	Lifetime incidence of subdural hematomas	- n=1 patient with SDH (clinical diagnosis group) + characteristic MRI. - overall incidence of SDH in GA1 patients = 4% (vs. 20-30% in literature) → GA1 should not routinely be a part of DD in case of unexplained SDH without imaging characteristics suggestive of GA1	Small sample size	Retrospective analysis	2-	Diagnostik Monitoring Therapie

			members with GA1, n=8 diagnosed by NBS						
Xiao et al. (2020) Front Genet; 11:496. Published 2020 May 20. doi:10.3389/fgene.2020.00496	Prenatal Diagnosis of Glutaric Acidemia I Based on Amniotic Fluid Samples in 42 Families Using Genetic and Biochemical Approaches		n=44	Prenatal diagnosis of GA1 based on amniotic fluid samples using genetic analysis and metabolite measurements (GC/MS + MS/MS)	Metabolite test: n=37 unaffected, n=7 affected. Mutation analysis: n=33 unaffected, n=6 affected (+ 1 patient for whom no precise diagnosis could be made). Metabolic markers (C5DC) were significantly higher in affected fetuses than in unaffected fetuses. The sensitivities of C5DC, C5DC/C8, and glutaric acid were 100%, and the specificities of C5DC, C5DC/C8, and glutaric acid were 91, 76, and 76%, respectively.		Indirectness (population differences)	2-	Diagnostik Therapie
Yahyaoui et al. (2020) Genes (Basel). 2020 Aug 29;11(9):E1018.	Metabolic Serendipities of Expanded Newborn Screening	Case series	n=4 patients with incidental findings on NBS.	Mutation analysis.	- Patient 2: Maternal GA1 mimicked a carnitine transporter deficiency. - Mutation analysis: c.1204C>T (p.Arg402Trp, pathogenic) and c.853-26_854del (p.?, probable pathogenic). - Clinically asymptomatic mother and child. - Therapy (mother) was started with protein restriction and carnitine supplementation.		Small sample size	3	Diagnostik
Zayed et al. (2019) Metab Brain Dis; 34(4):1231-1241	Clinical, biochemical, neuroradiological and molecular characterization of Egyptian patients with glutaric acidemia type 1		n=89 Egyptian patients, diagnosed based on clinical presentation (asymptomatic patients diagnosed by neonatal screening because of positive	Clinical outcome Biochemical analysis (GC/MS, MS/MS) Neuroradiological imaging (MRI) Mutation analysis	- Acute onset (72%), insidious-onset (19%), asymptomatic (9%) - Asymptomatic patients with significantly lower morbidity score. - Consanguinity in 64%, positively associated with C5DC level. - 34% with positive family history. - 69% with macrocephaly. - 93% HE (18% “massive”, 75% “high”), 7% LE - <u>Development</u>: All patients had variable degrees of developmental delay ranging from mild to severe. Mild cognitive delay (13%), moderate cognitive delay in 16%; 19% speech delay (mild), and 47% moderate speech delay, 34% severe speech delay.		Indirectness (population differences) Authors don`t specify the developmental delay or how it was conducted, no tests or scores are cited.	2-	Diagnostik Monitoring

			family history)		- MRI: damage of globus pallidus (in 89% of the patients), putamen (83%), caudate nucleus (63%), white matter changes in 14/17 patients. - 41 patients with mutation analysis: 25 variants - n=29 c.1204C>T in 15/41 patients - n=42 (homozygous in 21 patients) c.*165A>G (unknown clinical significance) - 6 new variants (c.320G > T, c.481C > T, c.572 T > G, c.78delG, c.1035delG, c.272_331del).				
Zhang et al. (2016) Clin Chim Acta; 453:75-79	Clinical and molecular investigation in Chinese patients with glutaric aciduria type I	Case series	n=5 patients diagnosed based on results of urinary organic acid testing and/or plasma acylcarnitine analysis.	Clinical outcome Mutation analysis Biochemical analysis	Age at onset of symptoms between 4 and 11 months, age at diagnosis between 4 and 12 months. n=4 patients with macrocephaly, n=3 with dystonia, n= 3 with instability of lifting up head, n=1 died at age 6M. 4/5 patients had protein-restricted diet. Mutation analysis: 2 novel (splice site) mutations (c.334G>T, IVS11-11A>G), 2 patients with homozygous mutations, 3 patients with compound-heterozygous mutations.		Indirectness (population differences)	3	Diagnostik
Zhang et al. (2017) Exp Ther Med. 2017 Feb;13(2):560-566	Clinical and laboratory analysis of late-onset glutaric aciduria type I (GA-I) in Uighur: A report of two cases	Case series	n=2	Clinical outcome Biochemical analysis Mutation analysis	1) 12Y female, non-consanguineous parents: intermittent head-ache (30-120 minutes) over 2M, every 3-5 days. - MRI: bilateral temporal lobe arachnoid cyst, focal patchy T2 flair high signals in semi-oval area, corner and anteroposterior horns of lateral ventricle (white matter degeneration). - Neurologic examination without abnormalities. 2) 6Y female, sister of 1); no clinical or MRI abnormalities. Biochemical analysis: HE phenotype in both patients, Mutation analysis: heterozygous c. 1204C >T (p.R402W) + c. 532G >A (p.G178R)		Small sample size	3	Diagnostik

					Treatment: low-fat, low-protein, high-carbohydrate diet, large doses of vitamin B2 (50 mg, tid), L-carnitine (100 mg/kg/day).				

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