Recommendations for diagnosing and managing individuals with glutaric aciduria type 1: third revision

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Summary

Glutaric aciduria type 1 is a rare inherited neurometabolic disorder of lysine metabolism caused by pathogenic gene variations in *GCDH* (cytogenic location: 19p13.13), resulting in deficiency of mitochondrial glutaryl-CoA dehydrogenase (GCDH) and, consequently, accumulation of glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and glutarylcarnitine detectable by gas chromatography/mass spectrometry (organic acids) and tandem mass spectrometry (acylcarnitines). Depending on residual GCDH activity, biochemical high and low excreting phenotypes have been defined. Most untreated individuals present with acute onset of striatal damage before age three (to six) years, precipitated by infectious diseases, fever or surgery, resulting in irreversible, mostly dystonic movement disorder with limited life expectancy. In some patients, striatal damage develops insidiously. In recent years, the clinical phenotype has been extended by the finding of extrastriatal abnormalities and cognitive dysfunction, preferably in the high excreter group, as well as chronic kidney failure. Newborn screening is the prerequisite for pre-symptomatic start of metabolic treatment with low lysine diet, carnitine supplementation and intensified emergency treatment during catabolic episodes, which, in combination, have substantially improved neurologic outcome. In contrast, start of treatment after onset of symptoms cannot reverse existing motor dysfunction caused by striatal damage. Dietary treatment can be relaxed after the vulnerable period for striatal damage, i.e. age 6 years. However, impact of dietary relaxation on long-term outcome is still unclear. This third revision of evidence-based recommendations aims to re-evaluate previous recommendations [1-3] and to implement new research findings on the evolving phenotypic diversity as well as the impact of non-interventional variables and treatment quality on clinical outcomes.

Synopsis

Pre-symptomatic diagnosis through newborn screening, early introduction and adherence to recommended maintenance and emergency treatment supervised by a multi-professional team in a metabolic centre can prevent striatal damage and hence substantially improve neurodevelopment and clinical outcomes in the majority of screened individuals with GA1.

Abbreviated title

Third revision of recommendations for management of glutaric aciduria type 1

References to electronic databases

Glutaric aciduria type 1: OMIM # 231670

Glutaryl-CoA dehydrogenase: EC 1.3.8.6

Abbreviations

AAM, amino acid mixture

C5DC, glutarylcarnitine

CSF, cerebrospinal fluid

D-A-CH, German, Austrian and Swiss Nutrition Societies

DBS, dried blood spots

GA, glutaric acid

GA1, glutaric aciduria type 1

GABA, gamma aminobutyric acid

GCDH, glutaryl-CoA dehydrogenase

GC/MS, gas chromatography/mass spectrometry

GRADE, Grading of Recommendations, Assessment, Development and Evaluation

GDG, guideline development group

MD, movement disorder

MRI, Magnetic Resonance Imaging

MRS, Magnetic Resonance Spectroscopy

MS/MS, tandem mass spectrometry

NBS, newborn screening

3-OH-GA, 3-hydroxyglutaric acid

SDH, subdural haemorrhage

SIGN, Scottish Intercollegiate Guidelines Network

WHO, World Health Organisation

Details of the contributions of individual authors

Some authors have already been involved in the initial guideline developmental process (2003-2006), the first publication of the guideline [3], the first revision and publication [2], and the second revision and publication [1], whereas others have contributed for the first time.

This third guideline revision followed the criteria of SIGN (*Scottish Intercollegiate Guideline Network; publication no. 50, 2014*) and GRADE (*Grading of Recommendations, Assessment, Development and Evaluation*). For this purpose, selection and formulation of guideline topics and systematic search and evaluation of the literature have been performed. The guideline development group (GDG) met to discuss levels of evidence, clinical relevance and benefit and harms for affected individuals and to formulate recommendations. Writing and review of draft versions of single recommendations and repeated discussions followed. Members of the GDG worked in sub-groups on three major topics, i.e. (1) diagnostic work-up, (2) metabolic maintenance, emergency treatment and management of neurologic manifestations, and (3) clinical monitoring. All GDG members have contributed to the manuscript which has also been reviewed and revised by external consultants. The following list specifies authors' involvement and contribution to different working groups.

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S. Kölker:	Working group 2, initial guideline group coordinator (2003-2015), writing of the draft manuscript
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Competing interest statement

Consideration of conflicts of interests followed a recently recommended procedure [4]. All authors declare that the answers to all other questions on the JIMD competing interest form are "NO". The authors confirm independence from sponsors. The GDG did not accept direct funding from medical product companies or company foundations.

Eight members (K. Grohmann-Held, I. Harting, J. Heringer-Seifert, M. Kallmes, S. Kölker, M. Krawinkel, M. Lindner, J. G. Okun) declare that they have no conflict of interest. Three members (S. Fleissner, G. F. Hoffmann, R. Posset) were consultants for a pharmaceutical company; five members (N. Boy, S. Fleissner, K. Sahm, E. Thimm, M. Walter) gave presentations during meetings organised by a pharmaceutical company; three members (D. Ballhausen, G. Hahn, R. Posset) received financial funding for research. Eight members (D. Ballhausen, F. Jochum, D. Karall, E. M. Maier, C. Mühlhausen, B. Plecko, J. Zschocke, S. vom Dahl) worked in the Advisory Board of a nutrition or pharmaceutical company. All conflicts of interests were assessed as minor or without any thematic relation to the guideline process. No moderate or serious conflict of interest was declared. An overview on all competing interests is available online (https://www.awmf.org/leitlinien/detail/ll/027-018.html). The content of this article has not been influenced by the sponsors.

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Details of ethics approval and patient consent statement

Not required.

Key words

Glutaric aciduria type 1; glutaryl-CoA dehydrogenase; guideline; management; newborn screening; therapy; monitoring

Data and material statement

Seven translated versions (English, French, Spanish, Portuguese, Arabic, Russian, Turkish) of the parental guide based on the guideline recommendations can be found at https://www.awmf.org/leitlinien/detail/ll/027-018.html.

Introduction

Glutaric aciduria type 1 (GA1, OMIM #231670) is an autosomal recessive neurometabolic disorder of lysine, hydroxylysine and tryptophan metabolism caused by inherited deficiency of glutaryl-CoA dehydrogenase (GCDH, EC 1.3.8.6) with an estimated worldwide incidence of 1:90.000 to 1:120.000 newborns [5-8] and over 600 affected individuals reported in the literature [9] since the first description in 1975 [10].

At least five populations with a higher carrier frequency (up to 1:10) and incidence (up to 1:250) are known i.e., the Amish Community in Lancaster County, Pennsylvania, United States [11], the Oji-Cree First Nations in Manitoba and Western Ontario, Canada [12], the Irish Travellers in the Republic of Ireland and United Kingdom [13], the Lumbee in North Carolina, United States [14] and the Xhosa and other subgroups of the South African population [15].

GA1 is caused by bi-allelic pathogenic variants in the *GCDH* gene on chromosome 19p13.13 which encodes a flavin adenine dinucleotide-dependent mitochondrial matrix protein catalysing the oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA in the degradative pathway of lysine, hydroxylysine and tryptophan [16,17]. So far, 290 (confirmed or likely) pathogenic variants have been published and listed in the Human Gene Mutation Database (data drawn on December 1st, 2021) [18,19].

GCDH deficiency results in accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid and glutarylcarnitine (C5DC) which can be detected in body fluids (urine, plasma, cerebrospinal fluid [CSF]) and tissues using gas chromatography/mass spectrometry (GC/MS) or electrospray-ionization tandem mass spectrometry (MS/MS; [20,21]), respectively.

Depending on the urinary GA concentration two biochemical subgroups have been arbitrarily defined, i.e., *low* (LE) and *high* (HE) excretors [20]. Residual GCDH activity of 3-30% is found in LE patients, , while HE patients show a residual activity of 0-2% [5,18,22]. The genotype correlates with the biochemical phenotype, but not with the clinical course in terms of risk for striatal injury and frequency of dystonic movement disorder (MD) [9,23,24]. However, HE patients (compared to LE) show increased frequency of extrastriatal abnormalities and higher intracerebral concentrations of GA and 3-OH-GA detected by ^{1}H-MRS [25,26], larger head circumference [27], increased risk for subdural haemorrhage (SDH) [28], and poorer cognitive outcome [29].

Most infants are asymptomatic or may develop unspecific neurologic symptoms like muscular hypotonia and delayed motor development, making a clinical identification of affected individuals difficult. Macrocephaly, being present at or shortly after birth, is a frequent (75%) but nonspecific finding with a low positive predictive value considering a 3% frequency of macrocephalic individuals in the general population, when referring to the 97th percentile of head circumference of the general population as the definition of macrocephaly [30,31]. Without treatment, 80-90% of infants will develop irreversible striatal damage during a vulnerable period of brain development (mostly between age 3-36 months, with individual reports until age 72 months) following an acute encephalopathic crisis precipitated by intercurrent febrile illness, or surgical intervention [9,24,32-34]. These crises cause acute striatal damage, particularly affecting the putamen and spreading from the dorsolateral to the ventromedial aspects, and, subsequently, a complex MD with predominant dystonia. Severe MD may progress to status dystonicus and often results in limited life expectancy due to secondary complications[5,24,35]. Although striatal damage is usually bilateral, unilateral striatal necrosis with concomitant hemidystonia has also been reported [36].

Besides *acute-onset,* also individuals with *insidious-onset* type of striatal injury without an apparent crisis have been observed in up to 50% of symptomatic patients in newborn screening (NBS) cohorts, mostly associated with deviations from dietary treatment recommendations [5,9,22,24,32,34,37-40]. In contrast to *acute-onset* MD, striatal injury in *insidious-onset* is often restricted to the dorsolateral putamen, dystonia is less severe, manifests later in infancy, and may manifest clinically after a latency period of several years after onset of magnetic resonance imaging (MRI) lesions. Additionally, also *acute-on-insidious* onset with a characteristic MRI pattern has been described for *insidious-onset* patients with an superimposed *acute onset* [41].

Some individuals have been diagnosed with first symptoms in adolescence or adulthood (*'late-onset')* with unspecific neurologic symptoms, such as headaches, vertigo, transient ataxic gait, reduced fine motor skills or fainting after exercise [25,42] characteristic brain MRI abnormalities, such as periventricular white matter abnormalities, frontotemporal hypoplasia, and subependymal nodules, while the striatum is unaffected [25,43,44]. It remains doubtful whether this proposed *late-onset* subgroup truly forms a disease variant, since extrastriatal MRI abnormalities are also found in the HE group, regardless of striatal damage during infancy. Some late diagnosed individuals may not develop symptoms, and several asymptomatic women ('maternal GA1') have been identified following work-up of the abnormal NBS results of their unaffected children [45-47].

Due to the predominant neurologic phenotype GA1 is considered a 'cerebral' organic aciduria; however, involvement of the peripheral nervous system [48] and the kidney in the disease course has recently extended the phenotypic complexity [49]. As a first extracerebral manifestation, increased frequency of chronic renal failure has been reported in adolescents and adults [5,49] which has also been demonstrated in animal model studies [50,51].

Disproving initial doubts on general treatability of the disease, metabolic treatment concepts have been developed and optimised during the last 40 years. Nowadays, GA1 is considered a treatable disorder. Evidence-based guideline recommendations have first been published in 2007 [3], and revised twice [1,2]. Metabolic maintenance treatment consists of a low lysine diet with administration of a lysine-free, tryptophan-reduced, arginine-fortified amino acid mixture (AAM) and oral carnitine supplementation. Intensified intermittent emergency treatment is recommended for catabolic episodes of intercurrent illness or surgery. If administered according to guideline recommendations, this combined metabolic treatment has dramatically reduced the frequency of acute encephalopathic crises and MD and increased the probability for an asymptomatic disease course in early diagnosed individuals [5,6,24,32,34,38,39,52-57], as recently demonstrated in a world-wide meta-analysis with 647 patients [9]. Dietary treatment has been demonstrated to be safe allowing normal anthropometric development until early adulthood in all but severely affected patients [27].

A few cases of malignant brain tumours have been described in individuals not treated according to recommendations [48,58-60]. Whether GA1 generally increases the risk of brain neoplasms – like in L-2-hydroxyglutaric aciduria, another cerebral organic aciduria [61] – remains to be elucidated.

Since C5DC can be detected in dried blood spots (DBS) by MS/MS based NBS and early treatment is neuroprotective, GA1 has been included in many national NBS panels including 24 countries of the European Union and Switzerland [62].

Although the clinical outcome of individuals with GA1 has been continuously improved during the last three decades, differences still exist in diagnosis and management of the disease. The aim of this third revision of

recommendations is to re-evaluate previous recommendations [1-3] and formulate revised and – for new topics – new recommendations for diagnosis and management based on the best evidence available, clinical experience and perspectives of affected individuals.

Methods

Guideline development

The GA1 guideline development process was initiated in 2003 and first published in 2007 [3]. The first guideline revision [2] was based on first results of a prospective follow-up study evaluating the clinical impact of the guideline recommendations [32]. The following second revision [1] implemented increasing evidence on effects of treatment quality on outcome, and new findings such as the role of arginine, or maternal GA1. This third revision is based on the results of a GDG meeting on 21st September 2021 in Kassel, Germany, as well as four virtual meetings, with participation of 23 international experts in metabolic medicine, child neurology, clinical biochemistry, genetics, nutrition, (neuro-)radiology, and psychology. Participation of 13 professional societies as well as a representative of a patient support group (Glutarazidurie e.V.) resulted in a representative GDG composition. Potential conflicts of interests were documented with maximum transparency. After finalization, the GDG received feedback from external experts and the guideline was legitimised by all participating professional societies as well as the E-IMD consortium (European Network and Registry for intoxication type metabolic diseases; https://www.eimd-registry.org). All 24 recommendations are summarised in **Tab. 1.**

Target Group

This guideline is addressed to experts from paediatric and adult metabolic medicine, child neurology, genetics, (neuro-)radiology, nutrition, dietetics, psychology, and provides information for neurology, laboratory medicine, NBS, transition medicine, social work as well as to all affected patients and their families, aiming at improving medical health care for all individuals with GA1. Since the GDG composition reflects health care systems of developed first world countries, its representativity and considerations may be limited for developing countries with limited access to medical health care facilities required to follow recommendations.

Consensus procedure

Relevant key questions were identified by interdisciplinary consensus procedure comprising the recommendations of the 2nd revision [1] and new key questions arising since then. A structured consensus process guided by moderation was conducted to achieve formal consensus. All key questions were systematically discussed by the GDG. For each recommendation, level of achieved consensus (and level of recommendation) included (1) the specific formulation of the recommendation and (2) the content of associated tables. Consensus was achieved for all recommendations and was strong (>95%) in 21/24 of them.

Systematic literature review

The methodology by SIGN (*Scottish Intercollegiate Guideline Network*; URL: http://www.sign.ac.uk) and GRADE Grading of Recommendations, Assessment, Development and Evaluation; [63] was used. For the period from 1975 to 2015, the literature review performed for the first two guideline revisions [1,2] was reviewed and re-evaluated. For the period from November 2015 to October 2021 a systematic review of the literature was carried out using Medline, Embase, the Cochrane Library, MedLink, and Orphanet databases. Internet searches were also performed on various websites including international and national societies for inborn errors of metabolism and those of support groups. Each working group selected and evaluated the literature before considered as evidence (**Suppl. Tab. 1-2**).

Grading of recommendations

Practice/Action-guiding recommendations support specific interventions based on a certain level of evidence which was assessed as high, moderate, low or very low by the GDG. According to methodologies of SIGN and GRADE grading of recommendations considered (1) level and consistence of evidence, (2) clinical relevance and experience, (3) balance of benefits and harms for affected individuals, (4) general preferences and perspectives of affected individuals, (5) ethical, legal and economic considerations and (6) general practicability thus resulting in recommendations likely to be implemented and acceptable. For maximum transparency, information on level of evidence, consistency of evidence, clinical relevance and rate of consensus are provided for each recommendation. For details see evidence table of systematic literature review (**Suppl. Tab. 2)**.

Levels of recommendations (according to SIGN and GRADE)

"Strong" recommendation for/against (Level A): Undesirable consequences **clearly** outweigh/do not outweigh desirable consequences. (1) Evidence is of high quality, (2) there is high degree of certainty that effects will be achieved in practice, (3) there are only few side effects of therapy, and (4) there is a high degree of acceptance among affected individuals. In some cases, strong recommendations were made based on only moderate or low levels of evidence but with high clinical relevance or benefit for affected individuals.

Recommendation for/against (Level B): Undesirable consequences **probably** outweigh/do not outweigh desirable consequences. (1) There are weaknesses in the evidence base, (2) there is a degree of doubt about the size of the effect that can be expected in practice, (3) there is a need to balance the upsides and downsides of therapy or (4) there are likely varying degrees of acceptance among affected individuals.

Recommendation for research or conditional recommendation for use restricted to trials (Level 0): Balance between desirable and undesirable consequences is closely balanced or uncertain.

Disclaimer

The proposed recommendations are not intended to serve as a standard of management and care for affected individuals. Standards of care are formulated on the basis of all clinical data available and are influenced by scientific progress. Adherence to recommendations will not ensure correct diagnosis and optimal outcome in

all patients. Final clinical assessments must be made by experienced healthcare professional(s) and should include discussions of diagnostic and therapeutic options with affected individuals and their families. However, these recommendations provide a rational basis for decisions in clinical management of GA1.

Alterations since the 2nd revision in 2016

To the best of our knowledge, none of the previous recommendations [1] has been proven invalid. However, grades of recommendations may have been adapted based on the criteria described above. Six new recommendations (#4, #13, #14, #19, #22 and #24) were formulated and one former 'statement' was changed to a recommendation (#8) resulting in a total of 24 recommendations which have been classified as [certified (n=2); modified (n=15); new (n=7)] in relation to the previous version. Also, a short version of the guideline is provided (**Suppl. Tab. 6**).

Diagnostic procedures

Differential diagnoses

GA1 is caused by biallelic pathogenic variants in the *GCDH* gene on chromosome 19p13.13 resulting in deficiency of the corresponding mitochondrial enzyme. Accordingly, diagnosis is confirmed by detection of a disease-causing genotype and/or significantly reduced enzyme activity. Other laboratory abnormalities, clinical signs, or symptoms may be suggestive but not confirming, including macrocephaly, acute encephalopathy, bilateral basal ganglia injury, MD, SDH and retinal haemorrhages, as well as elevated concentrations of GA, 3-OH-GA, and C5DC in body fluids.

Relevant differential diagnoses of GA1 comprise (1) benign familial macrocephaly, or communicating hydrocephalus, (2) other metabolic diseases associated with macrocephaly (e.g., Canavan disease), (3) hepatic and uraemic encephalopathies, (4) *metabolic stroke* in classic organic acidurias (methylmalonic and propionic aciduria), urea cycle defects (e.g., ornithine transcarbamylase deficiency), and mitochondrial disorders (e.g., Leigh syndrome), (5) non-metabolic encephalopathies (encephalitis, meningitis, intoxication, Aicardi Goutières syndrome), (6) multiple acyl-CoA dehydrogenase deficiency, glutaric aciduria type 3, severe ketosis, bacterial contamination, renal insufficiency, 3-hydroxyacyl-CoA dehydrogenase deficiency and pseudo-glutarylcarnitinemia (in medium-chain acyl-CoA dehydrogenase deficiency), and (7) asphyxia, HIV encephalopathy, infantile cerebral palsy or child abuse.

Biochemical differential diagnoses of elevated GA and 3-OH-GA concentrations are summarised in **Suppl. Tab. 4**.

	Recommendation #1 [modified 2022; strong consensus]
Level of recommendation: **A Strong recommendation**	When GA1 is suspected, (differential-) diagnostic work-up, development of treatment plans, appropriate education and training of affected individuals and their families should take place in a specialised centre experienced in managing inherited metabolic diseases. Affected individuals diagnosed elsewhere should be transferred to such centres without delay.
Level of evidence	One study (SIGN level 2++) has demonstrated positive effect of supervision by a

	metabolic centre [32].
Clinical relevance	High.

Newborn screening

GA1 has been included in the disease panels of MS/MS-based national NBS programs in a constantly growing number of countries worldwide [62].

Major aims: NBS aims at reducing the risk of developing irreversible neurologic disease due to striatal damage. Neonatal diagnosis and start of treatment strongly increase probability for an asymptomatic disease course [5,6,9,13,24,32,34,37-39,53,55-57,64-66].

Definitions: Population-wide *newborn* mass screening for GA1 is performed by MS/MS analysis of acylcarnitines in DBS whereas *high-risk* screening is performed in neonates with a known increased *a priori* risk, i.e. affected family member.

MS/MS: The diagnostic metabolite for GA1 is C5DC in DBS. Some laboratories additionally use ratios to other acylcarnitines as secondary parameters [67]. Introduction of multiple reaction monitoring (MRM) to MS/MS analysis increased sensitivity and reduced the rate of false-positive results (screening reports *of German Society for Newborn Screening*, 2004-2019). Urinary acylcarnitines have been analysed in single patients, but not been studied systematically as a screening method [68].

Cut-off levels: A C5DC value above the cut-off is considered a positive (abnormal) screening result and requires follow-up analysis. Each NBS laboratory defines the C5DC cut-off level based on its own methodology and patient population. Controlled studies defining pathological values of acylcarnitines do not exist.

Diagnostic pitfalls: NBS does not reliably identify all affected individuals, since some LE patients may show only slightly increased or normal C5DC concentrations with consecutively false negative NBS results [5,32,69-73]. Sensitivity for C5DC screening in Germany was 95% in recent studies, but with a discrepancy between HE (100%) and LE patients (75-84%) [5,29,32]. Thus, a negative NBS result does not unambiguously exclude the diagnosis of GA1. New analytic methods have been developed during the recent years to improve LE detection, such as improved LC-MS/MS or use of acylcarnitine ratios [74-76]. A carnitine loading test may increase diagnostic sensitivity, but systematic studies have not been performed.

Differential diagnosis: Increased C5DC concentration may also be caused by multiple acyl-CoA dehydrogenase deficiency, renal insufficiency [77], maternal GA1 (see **recommendation #4**) or pseudo-glutarylcarnitinemia in medium-chain acyl-CoA dehydrogenase deficiency [78].

Confirmation of a positive NBS result

Pathological NBS results should be repeated in the same DBS sample (and if possible by the same laboratory) and confirmed by one or more alternative techniques, including quantitative analysis of GA and 3-OH-GA in urine and/or blood with GC/MS [20,79-81], molecular genetic analysis of the *GCDH* gene [18,19], and analysis of GCDH enzyme activity in leukocytes or fibroblasts [82].

Normal urinary or plasma 3-OH-GA concentrations are not suggestive but do not reliably exclude GA1 since some LE patients intermittently may show concentrations within the normal range. A recent study has demonstrated a decrease of metabolite concentrations in a GA1 mouse model with variants in the *SUCGT* (succinyl-CoA:glutarate-CoA transferase) gene, but this has not been studied in GA1 patients [83]. In contrast, elevated levels of 3-OH-GA (usually in combination with elevated concentrations of GA) are highly suggestive for GA1. Pitfalls for organic acid analysis should always be considered (**Suppl. Tab. 4**).

The range of borderline or slightly increased 3-OH-GA concentrations alone cannot differentiate between LE patients, heterozygous carriers (not disease-causing) or even pre-analytical problems. Therefore, no treatment stratification depending on biochemical abnormalities is recommended and metabolic treatment should always be immediately initiated if 3-OH-GA is elevated, i.e., before genetic and/or enzymatic analysis confirms the diagnosis (**Fig. 1**). Although *insidious-onset* manifested later than *acute-onset* dystonia in a prospective national follow-up study, also single neonatal cases of striatal lesions developing MD within the first year of life have been reported [5,39].

Detection of a disease-causing genotype confirms the diagnosis and is relevant for genetic counselling of families and patients as well as for prenatal diagnostics. Sensitivity of genetic analysis is 98-99% [19]. For some *GCDH* variants a correlation with biochemical phenotype and residual enzyme activity has been reported, but not with the clinical phenotype and risk for striatal injury [5,18,23,24]. One case of a special *GCDH* variant with dominant-negative effect and abnormal NBS result has been reported. GCDH residual activity was 10-20% (thus, in the range of symptomatic GA1 subjects and significantly lower than other heterozygous individuals showing GCDH activity of >30%), and no clinical or neuroradiologic abnormalities were observed [84]. At present it is unclear whether treatment is indicated in these individuals. In general, heterozygous carrier status is not considered as clinically relevant since heterozygous individuals remain asymptomatic without treatment.

If only one (or no) known disease-causing variant is detected but other suggestive clinical, biochemical and/or neuroradiologic features are present, an (by standard analysis technique) undetectable *GCDH* variant should be considered and GCDH activity should be determined in leukocytes or fibroblasts. Significantly reduced GCDH activity will confirm the diagnosis, while normal activity (or values in the range of heterozygous carriers) will exclude it. In symptomatic LE individuals, residual enzyme activities of up to 30% have been reported [23,24]. In contrast to broadly available molecular genetic analyses the determination of GCDH enzyme activity is currently only available in the laboratory of Prof. Wibrand in Copenhagen, Denmark (analyses are run once every 1-2 months).

Targeted diagnostic work-up due to suggestive clinical, biochemical or neuroradiological signs

Targeted diagnostic work-up should be performed if suggestive clinical, biochemical and/or neuroradiologic findings are present or if the *a priori* risk for GA1 is elevated (e.g., due to an index patient in the family or a specific ethnic heritage). With increasing worldwide implementation of GA1 into NBS programs, targeted diagnostic work-up has become less relevant nowadays but is still essential for individuals born before this era, in countries without NBS programs, or for LE patients missed by NBS. Thus, in case of suggestive findings, a targeted diagnostic work-up should always be performed, even if NBS was normal.

Beside macrocephaly, suggestive clinical signs comprise acute neurologic manifestations (e.g., occurring during febrile illness or other catabolic states) like acute or chronic onset of MD in infants, gait abnormalities, or (truncal) muscular hypotonia [9,49,85-94]. Individuals with *late onset* form may present with unspecific neurologic signs like polyneuropathy, incontinence, headache, early-onset dementia, epilepsy, or tremor [25,44,48,58]. Neuroradiologic abnormalities occur frequently in all patients and are summarised in **Suppl. Tab. 3** [25,39,95-101]**.**

Methods: Targeted diagnostic work-up uses the same methods as confirmatory work-up of positive NBS results (**Fig. 1**). No systematic data or clinical experience is available for analysis of GA and 3-OH GA in CSF. Due to reduced sensitivity in individuals with secondary carnitine depletion and in LE patients, MS/MS analysis of acylcarnitines in DBS (and plasma) is of less importance for targeted diagnostic work-up (in contrast to NBS). In patients with normal C5DC in DBS, analysis of urinary C5DC is an alternative method but with low availability [102] and lower sensitivity than quantitative analysis of 3-OH-GA in urine by GC/MS [79]. Use of *in vivo* loading tests using lysine or prolonged fasting tests is potentially harmful and obsolete. Additional use of *in vitro* loading tests does not increase diagnostic sensitivity [103].

Diagnosis may also be established by molecular genetic testing *without* previous biochemical analysis [104].

Fig. 1 summarises the diagnostic algorithm for GA1.

	Recommendation #2 [modified 2022; strong consensus]
Level of recommendation: **A Strong recommendation**	Positive (abnormal) NBS results and/or suggestive clinical, biochemical and/or neuroradiological signs should be confirmed by diagnostic work-up, including quantitative analysis of GA and 3-OH-GA in urine and/or blood, and, if abnormal, molecular genetic analysis of *GCDH* gene and/or GCDH enzyme analysis in leukocytes or fibroblasts (**Fig. 1**).
Level of evidence	Moderate (SIGN level 1+ to 3). Consistency of evidence is high.
Clinical relevance	High.

Subdural haemorrhage and arachnoid cysts. GA1 is associated with an increased risk of developing traumatic or incidental SDH and hygroma. SDH manifests mostly during the first three years of life, with a peak in late infancy when extent of macrocephaly is maximal [28,95,101,105-109], however, macrocephaly is often 'relative' (disproportion between skull and brain with consecutive enlarged external CSF spaces) and clinically not apparent, see **recommendation no. 20**)Exact frequency of SDH in GA1 is unknown since affected individuals may remain asymptomatic. SDH may be mistaken as abusive head trauma [101,106,110,111] and thus might be a diagnostic pitfall. In all reported GA1 patients with SDH, additional characteristic neuroradiologic abnormalities were present, such as frontotemporal hypoplasia with widening of anterior temporal CSF spaces and the Sylvian fissure [28,101]. Systematic studies or case reports on prevalence of GA1 in individuals with *isolated* SDH do not exist. Bilateral, but not unilateral, arachnoid cysts have been described in some patients and may be suggestive for GA1 but have only been verified in one of two patients on craniotomy [112-115], and differentiation from frontotemporal hypoplasia is challenging.

	Recommendation #3 [modified 2022; strong consensus]

Level of recommendation: **A Strong recommendation**	In children with SDH/hygroma (fluid collections) in combination with further characteristic neuroradiologic signs (frontotemporal hypoplasia with widening of anterior temporal CSF spaces and the Sylvian fissure, **Supp. Tab. 2**), targeted diagnostic work-up (using the algorithm in **Fig. 1**) is **s**trongly recommended.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

Maternal GA1

In several cases, diagnosis of maternal GA1 was established following (normal) diagnostic work-up of an initially abnormal NBS of the mother's child. GA1 was not confirmed in the children and biochemical parameters normalised during the following weeks [25,45-47,116]. Affected mothers developed no or unspecific neurologic symptoms.

	Recommendation #4 [new 2022; strong consensus]
Level of recommendation: **0 Recommendation for research**	In children with a positive (abnormal) NBS result, but negative (normal) confirmatory diagnostic work-up, the mother **may** be informed about the possible condition of a maternal GA1 which can be further examined by targeted diagnostic work-up (**Fig. 1**).
Level of evidence	Moderate (SIGN level 2++ to 3). Consistency of evidence is moderate.
Clinical relevance	Unknown.

Metabolic maintenance treatment

Start of treatment

Combined metabolic treatment consists of maintenance treatment (low lysine diet, oral carnitine supplementation) and intermittent intensified emergency treatment (during episodes potentially inducing catabolism like febrile infections or perioperative fasting periods) and should be started immediately when GA1 is suspected (**Fig. 1**).

Treatment and follow-up require the experience and expertise of an interdisciplinary, multi-professional team at a centre experienced in managing inherited metabolic diseases. Such teams should include specialists in inherited metabolic diseases, child neurology, (neuro-)radiology, nutritional medicine and therapy, dieticians, nurses, physiotherapists, occupational therapists, speech therapists, psychologists and social workers. Supervision by such centres allows (1) implementation of metabolic maintenance treatment, (2) creation of age-adapted dietary protocols, (3) regular education and training of patients and their families, (4) availability of a 24/7 metabolic emergency service, (5) regular follow-up investigations and (6) detection of potential adverse treatment effects (e.g., malnutrition, failure to thrive due to inadequate diet).

Regular supervision by such centres significantly increases the probability of an asymptomatic disease course [32].

	Recommendation #5 [modified 2022; strong consensus]

Level of recommendation: **A Strong recommendation**	Metabolic maintenance treatment should be implemented and regularly evaluated by an interdisciplinary team in a specialised centre experienced in managing inherited metabolic diseases.
Level of evidence	High to moderate (SIGN level 1- to 2-). Consistency of evidence is moderate.
Clinical relevance	High.

Effectiveness of treatment

The vast majority of individuals remain asymptomatic if maintenance and emergency treatment are started in the newborn period before onset of symptoms and are continuously maintained according to the guideline recommendations [5,6,13,24,32,34,38-40,52,53,55-57,65,117-119]. This positive effect was recently confirmed in a meta-analysis including 647 patients worldwide [9]. The low lysine diet is safe and allows normal anthropometric development until early adulthood in most individuals while severe MD is associated with impaired weight and length development [27,34,52]. Quality of treatment has the strongest impact on neurologic outcome, and consequent adherence to guideline recommendations is associated with the best neurologic outcome: More than 90% of individuals adhering to recommended maintenance and emergency treatment remained neurologically asymptomatic, and rarely developed MD (7%). In contrast, non-adherence to emergency treatment resulted in (mostly severe) MD in 100% of cases, and non-adherence to maintenance treatment significantly increased the risk for (mostly mild to moderate) *insidious-onset* MD [5,32,120].

Effectiveness of treatment implemented *after* manifestation of neurologic disease is strongly limited has only been observed in single patients [22,24,30,35,37,88,91]. However, some individuals may benefit from prevention of progressive neurologic deterioration [85,86,90].

Dietary treatment

International recommendations and individualisation of treatment: Dietary recommendations considering age-dependent needs of a growing child have been developed by international organisations like World Health Organisation (WHO) or *German, Austrian and Swiss Nutrition Societies* (D-A-CH), are usually based on *safe level* (=mean+2 SD of daily required intake) and may vary substantially due to the use of different protein requirements and use of average versus safe levels. The GDG is mostly experienced in the use of revised safe levels [121] and D-A-CH recommendations (revised 2019) for calculating individualised dietary protocols that are therefore used for this guideline, have been used in many clinical trials and are associated with a positive outcome [5,6,27,32,40]. Recommendations for nutrient and energy intake in healthy children by D-A-CH were revised in (2019), and its recent version is similar to the previous recommendations of D-A-CH (2015) as well as the recommendations of the joint WHO/Food and Agriculture Organization (FAO)/United Nations University (UNU) expert consultation (World Health Organisation 2007) except for minimal differences in the first months of life. Dystonic patients may show need for increased energy intake requiring adaption of maintenance treatment to individual patient's needs [52,122,123], see also **Individuals with dystonic movement disorder**.

Principles of low lysine diet until age six years: Lysine is an essential amino acid and must therefore be provided by nutritional intake to allow normal growth. 'Diet' stands for adjusted oral intake of food aiming at influencing

the health state; 'nutritional therapy' aims at improving the identified nutritional problem considering individual needs including dietary treatment, education, counselling and monitoring [124]. The main goal of low lysine diet in GA1 is to *reduce* the daily intake of lysine, the quantitatively most relevant amino acid precursor of neurotoxic metabolites, while maintaining an adequate supply of all essential micronutrients (**Tab. 2** and **Suppl. Tab. 5**). In animal models, cerebral concentrations of GA and 3-OH-GA can be modulated by the amount of dietary lysine intake [125-127]. Since *in vivo* measurement of metabolites requires invasive methods, analogous data for individuals with GA1 are scarce and knowledge is based on a *post mortem* study [128]. However, ^{1}H-magnetic resonance spectroscopy allows for non-invasive quantification of cerebral GA and 3-OH-GA concentrations but has not been used for treatment adaption [26].

Compared to a low lysine diet, the approach of a *'low protein diet'* with limitation of protein intake concomitantly reducing lysine intake is less precise since lysine content in natural foods varies considerably, e.g., 2-4% (lysine/protein) in cereals and 9% (lysine/protein) in fish (**Suppl. Tab. 5**). Therefore, *direct* calculation of lysine intake instead of total natural protein intake is more precise, reduces day-to-day variability of lysine intake [122,123], and has been used in many clinical trials in combination with administration a lysine-free, tryptophan-reduced and arginine-enriched AAM aiming to provide adequate supply of essential amino acids and – with some product-specific variations – also minerals, trace elements and vitamins. This maintenance treatment (low lysine diet, AAM supplementation, carnitine supplementation) and intermittent emergency treatment has been associated with the most favourable neurologic outcome in many studies [5,6,24,32,38,40,52,57,65], including a meta-analysis of 647 patients [9]. In contrast, less pronounced clinical effect could be demonstrated in individuals calculating protein intake instead of lysine and omitting AAM [24,39,129]. In the recently published largest worldwide NBS cohort in the US, 47% of patients with a low protein diet developed a MD, while only 7% of patients with a low lysine diet developed MD thus confirming previous observations in the second largest NBS cohort in Germany [5,34].

Biochemical subtype and metabolic treatment: Although evidence is increasing on neuroradiological and clinical differences between HE and LE patients [25,28,29,98], treatment effects on these abnormalities has not been confirmed. Thus, metabolic treatment should not be stratified based on biochemical subtype.

	Recommendation #6 [modified 2022; strong consensus]
Level of recommendation: **A Strong recommendation**	A low lysine diet is strongly recommended in all patients up to the age of six years. To ensure sufficient protein intake, additional administration of lysine-free, tryptophan-reduced and arginine-enriched amino acid mixtures is strongly recommended.
Level of evidence	High (SIGN level 1+ to 2+). Consistency of evidence is high.
Clinical relevance	High.

Dietary treatment after age six years: Long-term outcome in GA1 is still poorly understood. Besides *acute-onset*, the *insidious-onset* and *late-onset* disease forms have been described with neurologic symptoms and correlating striatal and extrastriatal manifestations in MRI *without* a preceding crisis [5,9,22,32,34,37,39,41,43,44,58,98]. Within the 'window of vulnerability' during the first six years of life *insidious-onset* MD manifested significantly

later (median age 630 days) than the *acute-onset* form (median age 270 days) [5]. In contrast, individuals with *late-onset* form present during adolescence or adulthood with unspecific (non-striatal) neurologic symptoms.

The low lysine diet can be liberalised to a 'protein-controlled diet' using natural protein with a low lysine content and avoiding lysine-rich food (e.g., according to national recommendations like Optimix®, formulated by the *Research Institute of Child Nutrition*, Bochum, Germany), after age of six years since (1) the 'window of vulnerability' has ended and striatal injury is not manifesting anymore, (2) clinical impact of extrastriatal CNS abnormalities, that are frequently found even in early treated NBS patients, is unclear and (3) renal manifestation seems to be independent from treatment quality. However, continuation of lysine restriction is recommended since (1) clinical long-term course is unknown, (2) extra-neurologic (renal) manifestations in adolescent and adult patients starting in school age have been described [5,89], (3) extrastriatal abnormalities expressing chronic neurotoxicity are progredient [25] and malignant CNS tumours were found in single patients, however, of unknown causality [59], and (4) some late diagnosed adult patients show progredient neurologic symptoms such as polyneuropathy, epilepsy and dementia [25].

Of note, clinical effects and required intensity of lysine restriction in this age group are still unknown. In one of the largest NBS cohorts, individuals with protein-controlled diet showed age-appropriate anthropometric development until adulthood except for patients with severe MD [27], and none of the patients developed new motor symptoms after age six years, which was also confirmed in the large U.S. NBS cohort [34]. Thus, liberalization of dietary treatment seems not to be associated with a health risk, but is still variable in practice in the US and South America [130]. To prevent growth disturbance or malnutrition, the transition from low lysine diet to protein-controlled diet *after* the age of six years and the following period should be accompanied by regular dietary advice by nutritional experts.

	Recommendation #7 [modified 2022; strong consensus]
Level of recommendation: **B Recommendation**	After age six years, dietary treatment should follow an age-adapted, protein-controlled protocol which is based on safe levels for protein intake and avoids excessive intake of food with high lysine content. Dietary transition should be accompanied by regular dietary advice.
Level of evidence	High to moderate (SIGN level 2++ to 3). Consistency of evidence is moderate.
Clinical relevance	High.

Infant feeding: Breastmilk is physiological and beneficial for infants [131]. Initially, evidence for successful breastmilk feeding of babies with inherited metabolic diseases was limited to phenylketonuria (PKU) [132,133] but was recently extended to other intoxication-type metabolic diseases [134]. Breastmilk feeding in infants with GA1 is used worldwide and should be encouraged. The GDG is mostly experienced in breastmilk feeding on demand *after* administration of a lysine-free and tryptophan-reduced AAM thus limiting lysine intake in analogy to PKU [135]. This procedure has been used in several trials and is associated with beneficial clinical outcome [5,6,32,40,52]. Clinical experience with administration of AAM *after* breastmilk feeding is limited [136]. Since the amount of lysine in breast milk (86 mg per 100 mL [137]) and formula milk used for bottle feeding are known, daily lysine intake can be easily calculated.

Children with feeding problems: Those patients need close supervision of a metabolic dietitian and further supportive measures, such as tube feeding, pharmacotherapy or surgery (i.e., fundoplication, gastrostomy, jejunostomy) should be considered to sustain adequate energy supply.

Children with dystonic MD: Depending on the level of muscular activity, energy demand may be increased up to 130-150% (and beyond, especially in status dystonicus) in individuals with MD (personal communication, B. Assmann, Heidelberg). Anthropometric and nutritional status as well as amount of subcutaneous fat may be used as clinical parameters to guide the evaluation in a chronic setting. Urinary ketone bodies excretion should be monitored in status dystonicus. With increased sweating and breathing, water and salt are lost and need to be replaced on an individual basis. However, also decreased energy demand has been reported in individuals with severe MD due to immobility [138]. Therefore, intensive clinical and dietary monitoring is necessary to adapt energy intake to maintain anabolism and avoid catabolism. Individuals with severe MD are also at increased risk of aspiration pneumonia, feeding problems, malnutrition, and growth impairment [6,27,52,122,123] and show increased mortality rates compared to patients with mild or moderate MD [5].

Education: The clinical success of metabolic treatment ([9] and **recommendation #5**) critically depends on sufficient information and education of parents, affected individuals and caregivers. It is essential that they receive continued support and education from the interdisciplinary metabolic team. Based on the guideline recommendations, a pragmatic parental guide has been developed, revised and translated into six languages including English, Spanish, Portuguese, French, Russian and Arabic (https://www.awmf.org/leitlinien/detail/ll/027-018.html).

Arginine: In contrast to lysine, the semi-essential amino acid arginine is synthesised within the body. Only 40% of exogenous dietary arginine reaches circulation after intestinal digestion and metabolism [139]. Comparable to lysine, arginine content in natural protein varies considerably. Arginine intake in a GA1 patient is particularly determined by the amount of arginine in lysine-free, tryptophan-reduced AAM and natural protein in their diet, but recommendations for optimal arginine intake have neither been formulated for healthy children nor for patients with GA1.

In theory, the competitive mechanism of lysine and arginine for cerebral uptake via the CAT1 transporter across the blood brain barrier can be exploited for treatment which has been named 'complementary dietary therapy' [38,40]. However, only supraphysiologic doses of arginine supplementation used in the animal model resulted in additional decrease of GA and 3-OH-GA concentrations [126]. In the same study, low lysine diet was shown to be much more effective in reducing cerebral levels of neurotoxic metabolites. In a recent study in healthy adults, IV administration of high dosed arginine (300-600 mg/kg/d, i.e., higher than in patients with urea cycle disorders) reduced lysine oxidation in addition to lysine restriction [140]. Potential adverse effects of arginine administration comprise metabolic acidosis or arterial hypotension.

The arginine content in commercially available AAMs in Germany and, consequently, daily arginine intake may vary considerably during the first year of life while less variability exists in AAMs used for older children. In 34 patients whose arginine intake through AAM differed during the first year of life (90 vs. 48 mg/g protein) and converged later, clinical outcome was similar [40]. In contrast, several studies showed a positive impact of dietary therapy with administration of lysine-free, tryptophan-reduced and arginine-fortified AAM on outcome [6,24,32,40,52]. Thus, arginine intake within the low lysine diet could partially contribute to the overall beneficial

effect of nutritional therapy. In recent large NBS cohort studies and a meta-analysis, outcome of patients receiving dietary treatment with lysine restriction and supplementation with a lysine-free, tryptophan-reduced and arginine-fortified AAM (plus oral supplementation of carnitine and emergency treatment) was superior to protein restriction without AAM supplementation (plus oral supplementation of carnitine and emergency treatment) with regard to prevention of MD, as well as morbidity and mortality [5,9,34]. Clinical impact of decreased arginine plasma concentrations observed during acute illness, but also common in acutely ill children without GA1, is unclear [141]. No evidence exists for beneficial clinical effects of an additional arginine supplementation as a single amino acid in addition to AAM for maintenance or emergency treatment.

	Recommendation #8 [new 2022; majoritarian approval]
Level of recommendation: **0 Recommendation for research**	Since there is no evidence for clinical benefit of the use of arginine as a single amino acid for maintenance or emergency treatment in addition to arginine intake via natural food and AAM, an additional arginine supplementation is not recommended.
Level of evidence	Moderate (SIGN level 2+ to 2-). Consistency of evidence is moderate, selective effect of arginine from AAM cannot be evaluated.
Clinical relevance	High.

Pharmacotherapy

Carnitine supplementation: Besides its essential role for mitochondrial long-chain fatty acid transport, carnitine is important for physiological detoxification by removing toxic CoA compounds that accumulate in organic acidurias. In GA1, accumulating glutaryl-CoA conjugates with carnitine forming non-toxic, water-soluble and renally excretable C5DC, but increasing accumulation of glutaryl-CoA is proposed to reduce the intracellular CoA pool, a central cofactor in intermediary metabolism [142]. The resulting secondary carnitine depletion is frequently found in untreated patients [37,91,142,143] and recently, cerebral deficiency of free carnitine was demonstrated in a rat model for GA1 [127]. Oral carnitine supplementation can compensate carnitine depletion as demonstrated in a mouse model [126] and has positive effects on oxidative stress parameters [144,145]. Carnitine supplementation is associated with risk reduction for developing striatal injury and MD in early diagnosed individuals [5,6,32,38,53,55,57,65] and reduces mortality in symptomatic individuals [24]. As a consequence, carnitine supplementation is recommended lifelong [1], although no randomised controlled studies evaluating the selective effect of carnitine on clinical outcome are available [146,147]. In general, compliance rate of oral carnitine supplementation is good [24,30,37,55] comprising 100% of patients aged 0-6 years in a recent large NBS cohort study in Germany [5], and also the majority of older individuals [27].

An initial oral dosage of 100 mg carnitine/kg per day divided in three doses is recommended and then individually adjusted to maintain the plasma or DBS free carnitine concentration within the normal range [6,55]. No severe adverse effects have been reported so far, and dosage reduction due to diarrhoea and fishy odour may only be necessary in single patients. Fishy odour, caused by metabolization of carnitine to trimethylamine (TMA), was reduced by treatment with riboflavin in single patients [148].

One experimental study demonstrated increased production of trimethylamine-N-oxide (TMAO), a pro-atherogenic metabolite of carnitine formed by intestinal microbiotic metabolism, after carnitine intake from red meat [149]. Whether long-term carnitine supplementation in GA1 is associated with an increased risk for developing atherosclerosis is unknown, and a vegetarian-based diet as used in GA1 seems to be protective. At present, the benefits of carnitine supplementation are believed to most probably outweigh the potential risks.

	Recommendation #9 [modified 2022; strong consensus]
Level of recommendation: **B Recommendation**	Carnitine should be supplemented lifelong aiming to maintain the concentration of free carnitine in plasma or dried blood spots within the reference range.
Level of evidence	High to moderate (SIGN level 2++ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

Riboflavin: Although biochemical effects (decreased GA and 3-OH-GA concentrations) following riboflavin supplementation have been reported [143,150,151], there is no evidence that riboflavin improves the clinical outcome [24]. No standardised protocol for evaluation of riboflavin responsiveness exists, and no predictive genotype is known. Riboflavin can cause adverse gastrointestinal symptoms such as nausea and abdominal pain.

Neuroprotective agents: Drugs used with neuroprotective intention, such as antiepileptics (e.g., phenobarbitone, topiramate, carbamazepine), creatine monohydrate, glutamate receptor antagonists (e.g., dextromethorphan), and antioxidants are not beneficial in GA1 [35,55,152,153].

Tab. 2 summarises recommendations for metabolic maintenance treatment.

Emergency treatment

Since maintenance treatment alone is not sufficient to avoid acute encephalopathic crises, it is essential to conduct intermittent intensified emergency treatment during potentially catabolic episodes, e.g. febrile illness, or perioperative/peri-interventional fasting periods during the first six years [6,32,37,39,54,55]. In the last three decades, emergency treatment has been established and recommended as an essential part of combined metabolic treatment [1,5,28,32,34,38,53,57,65,154-157]. Quality of emergency treatment is the strongest predictor of neurologic outcome, as demonstrated by several studies and a recent meta-analysis [5,9,34,38]. While individuals receiving adequate emergency (and maintenance) treatment mostly remain asymptomatic, inadequate or delayed start of emergency treatment results in a high risk of striatal injury with mostly severe MD [5,9,32,157]. To avoid this, possible causes for delays should be identified, and preventive strategies should be followed (**Tab. 3**). Emergency treatment should be initiated immediately, with low clinical suspicion and intensified stepwise.

Principles: Emergency treatment follows elementary principles based on promoting anabolism and initiating specific detoxification measures that have been established for *intoxication-type* metabolic diseases [158,159]: (1) prevention or reversal of (potential) catabolism by administration of a high-energy intake (plus insulin in case of hyperglycaemia and/or lipids if required); (2) reduced production of neurotoxic GA and 3-OH GA by transient decrease or omission of natural protein for 24 (-48) hours; (3) support of endogenous detoxification

mechanisms and prevention of secondary carnitine depletion by increased carnitine supplementation and (4) if applicable, correction of dehydration, electrolyte imbalance, and altered pH status via IV fluids.

Start of emergency treatment: acute encephalopathic crises may occur during *any* febrile illness, or perioperative fasting periods during the striatal 'window of vulnerability' (age 0-6 years). Alarming symptoms include conditions that accelerate catabolism, such as fever, repeated vomiting and diarrhoea (with or without fever), and (new) manifestation of neurologic symptoms (i.e., reduced consciousness, muscular hypotonia, irritability, rigor, dystonia, chorea), which should all result in immediate start of emergency treatment. After age of six years, no acute striatal injury has been reported [9,24,30,37,55] and clinical impact of emergency treatment is unclear, although not systematically studied. However, since potential subclinical cerebral injury during catabolic crises cannot be excluded the threshold to start emergency treatment should be low in these individuals [1,32,39].

	Recommendation #10 [certified 2022; strong consensus]
Level of recommendation: **A Strong recommendation**	It is strongly recommended to start emergency treatment immediately and to perform it aggressively in any case of febrile illness, , or alarming symptoms as well as during perioperative management within the vulnerable period for striatal injury (up to age six years).
Level of evidence	High to moderate (SIGN level 1+ to 4). Consistency of evidence is high.
Clinical relevance	Very high.

Outpatient emergency treatment

Outpatient emergency treatment may be conducted at home if the individual is clinically well despite fever, the body temperature is below 38.5 °C (101 °F), oral intake is tolerated and no alarming symptoms (i.e., alteration in level of consciousness, diarrhoea, vomiting, irritability, hypotonia, dystonia) are present. The child should be reassessed every two hours for level of consciousness, fever, and feeding tolerance requiring adequate training and education of the parents and reliable telephonic consultation by the supervising centre in case of emergency. For sufficient energy supply, parents may apply maltodextrin solutions or comparable carbohydrate supplementations orally or via tube feeding. If body temperature rises above 38.5 °C, antipyretics such as ibuprofen or paracetamol should be administered as reduction of fever reduces energy requirement and has a positive effect on well-being, pain and feeding tolerance. If outpatient emergency treatment is well tolerated and alarming symptoms do not occur, maintenance treatment should be reintroduced stepwise during the next 48 (-72) hours.

Tab. 4 summarises recommendations for outpatient emergency treatment.

Inpatient emergency treatment

Individuals should be transferred to the supervising metabolic centre or the closest local hospital (under supervision of the metabolic centre) without delay for immediate start of inpatient emergency treatment if alarming symptoms develop such as recurrent vomiting and/or diarrhoea, reduced feeding tolerance or intake of nutrients, high fever or suspicious neurologic signs.

Tab. 5 summarises recommendations for inpatient emergency treatment.

Emergency treatment after age six years

Although acute encephalopathic crises have not been reported after age six years [6,9,24,30,32,55], the possibility that febrile illness or surgical procedures may cause subclinical cerebral damage in this age period cannot be excluded. For this reason, emergency treatment after age six years may be administered during episodes of severe illness or perioperative management in analogy to ET in younger patients with age-adapted glucose (age 7-10 years: 6-8 g/kg/24h or 4-6 mg/kg/min; age 11-15 years: 4-7 g/kg/24h or 3-5 mg/kg/min; >16 years: 3-5 g/kg/24h or 2-4 mg/kg/min) and fluid supply. Clinical effect of emergency treatment in adolescents and adults has not been systematically studied, and only case reports are available [160,161].

	Recommendation #11 [modified 2022; consensus]
Level of recommendation: **0 Recommendation for research**	Emergency treatment after age six years can be administered during episodes of severe illness or perioperative management in analogy to the age group 0-6 years with individual adaptation of glucose and fluid intake.
Level of evidence	Low (SIGN level 3). Consistency of evidence is low.
Clinical relevance	Moderate to high.

Peripartum management in women with GA1

Systematic analyses on the effectiveness or necessity of emergency treatment during the peripartum period are not available and therefore, specific recommendations cannot be formulated. Uneventful clinical course for mother and child has been reported in two women receiving emergency treatment during the peripartum period [160,162], but also in women not receiving emergency treatment [46].

Neurologic complications

Major neurologic complications comprise *acute* or *insidious-onset* of dystonic MD and SDH/hygroma (mostly within the first three years of life). Prevalence of epilepsy was not increased in early treated individuals of the two largest NBS cohorts worldwide, but has been reported in symptomatic patients not identified by NBS [5,34,89].

Management of movement disorders

Striatal injury results in a complex MD mostly manifesting as dystonia (and/or chorea) with superimposed muscular hypotonia. With age, dystonic MD might evolve from being mobile to fixed and might be associated with akinetic-rigid parkinsonism or spasticity [24,32,37,55,153,163]. Dystonia reduces quality of life, causes pain and possibly life-threatening crises (status dystonicus). Severe dystonia is associated with increased mortality [5].

	Recommendation #12 [certified 2022; consensus]
Level of recommendation: **A Strong**	Diagnosis and therapy of neurologic (i.e., movement disorder, symptomatic epileptic seizures) or neurosurgically treatable manifestations (SDH) should be managed by a neuropaediatrician/neurologist and/or neurosurgeon in close

recommendation	cooperation with metabolic specialists.
Level of evidence	High to moderate (SIGN level 2++ to 3).
Clinical relevance	High.

Dystonia rating scales

Evaluation of dystonic MD should comprise clinical localisation and severity. The *Barry-Albright Dystonia Rating Scale* [164,165] has been used in some studies [32,166], but may be of limited use in infants and young children since it likely underestimates the severity of MD in this age group due to severe truncal hypotonia [32]. The *Fahn-Marsden Dystonia Rating Scale (FMDRS)* has been used in hyperkinetic MD including cerebral palsy and is recommended for assessment of generalised dystonia, but does not assess individual body areas and has not been evaluated for GA1 [167,168].

Drug therapy

Dystonic MD is generally difficult to treat, and evidence regarding the effectiveness of specific drugs is scarce [169] making a specific recommendation for treating MD impossible. Most frequently used substances are listed below.

Baclofen: Baclofen is a derivative of gamma aminobutyric acid (GABA) and a centrally active muscle relaxant increasing spinal presynaptic inhibition and thus, decreasing muscle tone. Together with benzodiazepines, baclofen (as mono- or combination therapy) is the mostly used and apparently effective drug for long-term treatment of MD in GA1 [37,153], and dosing should follow general recommendations. In younger children with prominent axial hypotonia, use of baclofen may be limited due to worsening of muscular hypotonia. In several studies, also intrathecal administration of baclofen was successful if oral treatment was ineffective [35,170-172].

Benzodiazepines: Diazepam and clonazepam are often used in combination with baclofen and showed positive effects in more than 90% of symptomatic individuals [35,37,153]. Dosages should be administered according to general recommendations. To prevent tachyphylaxis, intermittent treatment may be necessary.

Zopiclone and Zolpidem: Zopiclone is a cyclopyrrolone with sedative, hypnotic, anxiolytic and muscle-relaxant qualities. In contrast to other benzodiazepines, its pharmacodynamic effect is non-selectively mediated by the GABA-$_A$ and GABA-Ω-(BZ1 and BZ2) receptor complex and modulation of chloride channel with a low risk of developing tolerance and addiction. Treated individuals do not show increased daytime sleepiness but, in contrast, are more relaxed and awake during the day as they are less affected by their MD during night-time. Cautious dose adaption and stepwise reduction is important, preferably provided in an inpatient setting. Positive effects of zopiclone, primarily used in non-metabolic dystonia, were demonstrated by reducing the hyperkinetic elements of MD and muscle tone [173].

Zolpidem, an imidazopyridine, is a benzodiazepine-like drug with hypnotic qualities and an agonist with high affinity to Ω-(BZ1) receptor subunit of the GABA-$_A$ receptor. It showed positive effects in a study with 34 dystonic adults, particularly on generalised dystonia and dystonia primarily affecting the hands. Effects were shown to be comparable with trihexyphenidyl [174].

Anticholinergic drugs: If treatment with baclofen and/or benzodiazepines is not effective or adverse effects occur, anticholinergic drugs may be considered as second line medication. Evidence on trihexyphenidyl is heterogenous. It was shown to be effective in individual cases [169], also in children with secondary dystonia [175,176]. A recently published review assessed trihexyphenidyl as possibly ineffective in patients with dystonic cerebral palsy [170]. Some adverse effects (e.g., blurred vision and dry mouth) usually are temporary whereas memory loss and confusion mostly persist and require dosage reduction. Ocular tonometry should be regularly performed in adults.

Botulinum toxin: Botulinum toxin type A, usually administered every three to six months, was successfully used to prevent hip dislocation and reduce limb dystonia [169]. Some individuals may develop antibodies against the toxin requiring cessation of treatment [177].

Gabapentin: Gabapentin modulates voltage-dependent calcium channels reducing excitatory neurotransmission in the CNS. It decreases muscle tone, has additional analgetic and antiepileptic qualities and had positive effects on dystonia, pain, quality of life and sleep in a retrospective study with 69 children without GA1 [178].

Drugs without benefit or adverse effects: In the past, also anticonvulsive medication has been used for treating MD in GA1 [35,37,153]: *Vigabatrin* and *valproate* showed clinical benefit in 10-25%. *Vigabatrin* may induce peripheral visual field defects and (mostly reversible) T2-hyperintensities in pallidum, thalamus and brainstem as putative side effects. *Valproate* may influence mitochondrial acyl-CoA/CoA ratio negatively. Therefore, these drugs should not be used for treatment in GA1. In the clinical experience of the GDG, *Carbamazepine*, *L-DOPA* and *amantadine* were ineffective.

Neurosurgery

Stereotactic surgery (pallidotomy) has been reported for three severely dystonic individuals with GA1. In two patients, clinical outcome was poor [55], whereas short-term improvement of dystonia was reported in another [179]. Data on long-term outcome after pallidotomy are not available. Bilateral deep brain stimulation of the internal globus pallidum reduced dystonia and slightly improved motor function in one patient [180] while minor improvement was also observed in a patient with atypical hemi-dystonia due to unilateral striatal necrosis after acute encephalopathic crisis [36]. However, no effect was detected in another patient with classical, severe *acute-onset* MD (*personal communication Dr. Cif, Montpellier*). Although positive effects on pain scale were reported [181], disparate motor outcome with slight improvement but also decline after deep brain stimulation was observed in patients with heredodegenerative dystonia including two GA1 patients [182]. A recent review, however, not including GA1, showed a positive effect primarily in 52 children with primary dystonia (e.g., *DYT1*-associated) in contrast to heterogenous outcome in 24 individuals with secondary dystonia [183].

Orthopaedic treatment

In a retrospective study 30% of 114 symptomatic patients underwent surgery due to orthopaedic complications (e.g., scoliosis, hip dislocation) [184].

Epilepsy

Prevalence of epilepsy was not increased in early treated individuals of the two largest NBS cohorts worldwide [5,34], but was reported in single late diagnosed patients [89]. Seizures are particularly reported during or shortly after an acute encephalopathic crisis [24,35,37,55,152] but dystonic MD may also be mistaken as seizures [185]. Studies on effectiveness of antiepileptic agents do not exist. Therefore, choice of treatment should follow seizure semiology and EEG patterns. *Valproate* and *vigabatrin* should be avoided due to their risk of developing mitochondrial dysfunction.

Subdural haemorrhage and arachnoid cysts

*Neurosurgery (see also **recommendation #12**):* Only a few older reports of individuals with GA1 undergoing neurosurgical procedures to treat arachnoid cysts and/or SDH are available [109,112,114,115]. Postoperative neurologic outcome was mostly poor, and symptoms often worsened. In addition, neurosurgical interventions in undiagnosed and untreated individuals increase the risk for acute encephalopathic crisis. Perioperative metabolic management should be based on **recommendations no. 10 and 11** for emergency treatment and be supervised by a specialised centre experienced in treatment of inherited metabolic diseases.

Vaccinations

Systematic studies on vaccination in individuals with GA1 do not exist. Importantly, besides upper respiratory tract infections, gastroenteritis, pneumonia and meningitis are the main trigger factors for developing acute encephalopathic crises [24] and quality of preventive emergency treatment has the strongest impact on neurologic outcome. Since reduction of potential risk factors for developing acute encephalopathic crisis is of essential importance immunization according to national recommendations should be performed in individuals with GA1 without any limitations. The GDG has not experienced any complications in GA1 patients in relation to vaccination since implementation of NBS. In single cases without NBS, GA1 was unmasked by febrile reactions after vaccination [186]. For treatment of febrile reaction to vaccinations see **recommendations #10** and chapter 'emergency treatment'.

	Recommendation #13 [new 2022; strong consensus]
Level of recommendation: **B Recommendation**	All patients with GA1 should be vaccinated according to national recommendations.
Level of evidence	Low to moderate, since systematic data are not available (SIGN level 2- to 3) but level of evidence on association of febrile illness with development of acute encephalopathic crises and strong impact of preventive emergency treatment on outcome is high (1- to 2+). The recommendation is based on clinical experience of the GDG and the high clinical relevance.
Clinical relevance	High.

Education concomitant to treatment

According to the German-Nutrition Care Process (G-NCP) 'process-guided nutrition therapy' comprises nutrition assessment, diagnosis, intervention, monitoring and evaluation as well as regular interaction with the

treatment team [124] aiming at optimizing treatment quality. In GA1, treatment quality is the prognostically most relevant factor and should therefore be regularly discussed in detail with patients and their families to ensure sufficient understanding and compliance [5,9]. Systematic education comprises information on pathogenesis, clinical course, treatment and prognosis and should include written information (parental guide, emergency card, dietary treatment plans).

Regular education and consultation help to improve outcome and quality of life and were also demanded by affected families as well as the patients' representative in the GDG [187].

	Recommendation #14 [new 2022; strong consensus]
Level of recommendation: **B Recommendation**	Age-specific education and information of affected patients and their families on disease course, treatment and prognosis as well as socio-legal advice and evaluation of quality of life should be regularly provided by an interdisciplinary team including experts in metabolic medicine, nutritional therapy, physiotherapy, social-advice and psychology.
Level of evidence	Moderate (SIGN level 3). Consistency of evidence is high.
Clinical relevance	High.

Clinical monitoring

General aims

Biomarkers predicting outcome in GA1 are not known. Clinical monitoring and regular follow-up examinations aim at evaluating and controlling effectiveness of treatment, assessing the patient's development and clinical status, adapting dietary treatment plans, and detecting new symptoms, complications or side effects of maintenance and pharmacologic treatment. Recommended parameters for monitoring should (1) be reliable and predictive for outcome, (2) allow therapeutic decisions, (3) have acceptable reproducibility, (4) be sufficiently affordable, and (5) practical [188] and should include expertise from paediatricians, metabolic specialists, nutritional therapists and dietitians as well as consultations from other specialities (e.g., neuropaediatricians, psychologists, physiotherapists, speech therapists, occupational therapists and social workers).

Tab. 6 summarises recommendations for clinical monitoring.

	Recommendation #15 [modified 2022; strong consensus]
Level of recommendation: **A Strong recommendation**	Therapeutic effectiveness and adverse side effects should be monitored by regular follow-up investigations and intensified in case of symptom progress or non-adherence to treatment recommendations. For recommended endpoints of clinical monitoring see recommendations **#17-20, 23, 24** and **Tab. 6**.
Level of evidence	High to moderate (SIGN level 1+ to 4).
Clinical relevance	Depending on each endpoint.

Biochemical monitoring

Organic acids: Quantification of urinary GA and 3-OH-GA biochemically confirms the diagnosis GA1 and classifies patients as HE or LE. While GA and 3-OH-GA remain elevated in most patients, also initial decrease in HE patients has been reported after start of maintenance treatment [33,37,38,55], but not in LE [152]. A subgroup of HE patients (termed i*ntermediate*) with moderately elevated GA concentrations prior to treatment (100-1000 mmol/mol creatinine) shows decrease to the range of LE under maintenance treatment [29].

Urinary or plasma concentrations of GA and 3-OH-GA do not correlate with the clinical course, risk for developing *acute-* or *insidious-onset* MD and renal function and therefore are not useful as biomarkers [5,9,23,24,52,53,57]. Clinical impact of more frequent extrastriatal abnormalities and increased *in vivo* concentrations of intracerebral GA in HE patients is unclear [25,26]. Moreover, HE phenotype seems to be a risk factor for long-term cognitive impairment, while individuals with LE and intermediate phenotype showed normal development, as recently demonstrated [29]. However, differences between HE and LE are not influenced by treatment quality (see 'Biochemical subtype and maintenance treatment').

	Recommendation #16 [modified 2022; strong consensus]
Level of recommendation: **B Recommendation**	Analysis of urinary concentrations of GA and 3-OH-GA should not be used for monitoring or adaption of treatment.
Level of evidence	Moderate to high (SIGN level 1+ to 3). Consistency of evidence is high.
Clinical relevance	Low.

Amino acids: Quantitative analysis of plasma amino acids aims at evaluating supply with essential amino acids in patients with a low lysine diet [122,123]. There is no clear-cut correlation between plasma lysine concentrations and lysine intake [40,52]. Although the 'optimal' lysine concentration within the age-specific normal range is unknown, concentrations of essential amino acids in patients on a low lysine diet with AAM supplementation and favourable neurologic outcome have shown to be mostly within the normal range [34,52]. Plasma amino acids profiles may furthermore be helpful for detecting deviations from maintenance treatment recommendations (e.g., too low/ high lysine/ protein intake or feeding problems) that are associated with an increased risk for *insidious-onset*-dystonia [5,9].

Since implementation of lysin-free, tryptophan-reduced AAMs, tryptophan deficiency has not been reported in individuals receiving these AAMs. If tryptophan deficiency is clinically suspected, plasma tryptophan level should be measured using HPLC or MS/MS as tryptophan cannot be measured accurately by conventional amino acid analysis [189,190].

	Recommendation #17 [modified 2022; strong consensus]
Level of recommendation: **A Strong recommendation**	Concentrations of plasma amino acids should be regularly quantified in patients with low lysine diet (3-4 hrs postprandially) and be maintained within the age-specific normal range (**Tab. 5**).
Level of evidence	Moderate (SIGN level 2++ to 4). Consistency of evidence is high.

Clinical relevance	High.

Carnitine status: Carnitine supplementation compensates secondary depletion of free carnitine and, in combination with dietary treatment, has a positive impact on neurological outcome [6,9,24,30,32,34,37,142]. Selective effect of carnitine on outcome remains unknown. Carnitine status also provides useful information on treatment compliance. There are no systematic analyses on differences between free carnitine concentrations in plasma vs. DBS. Internal analysis of 99 samples (metabolic laboratory Heidelberg) showed a linear correlation of analysis in DBS (unbutylated MS/MS method) and plasma (butylated photometric analysis), and therefore both methods are feasible. However, use of butylated method in DBS may result in false-high concentrations of free carnitine (personal communication, Prof. Okun, Metabolic Laboratory Heidelberg, September 2021). Plasma concentration of carnitine peaks 2-4 hours after intake [191] and thus, analysis as 12 hours trough level is recommended. Plasma concentrations of carnitine usually are within the upper (normal) range if administered according to recommendations in **Tab. 2** [52,53].

	Recommendation #18 [modified 2022; strong consensus]
Level of recommendation: **B** **Recommendation**	Concentration of free carnitine in plasma or dried blood spots should be monitored regularly in all individuals with GA1. Trough level concentration of free carnitine (at least 12 hours after last administration) should be maintained within the reference range.
Level of evidence	Moderate to high (SIGN level 1+ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

Acylcarnitine profile: C5DC concentrations increase markedly with carnitine supplementation [7,21,72], but regular analysis of C5DC or other acylcarnitines in DBS or serum are not useful for monitoring.

Renal function

Increased frequency of chronic renal dysfunction in adolescent and adult patients has been reported as a new, extra-neurologic disease manifestation appearing independently of the neurological phenotype [49]. Prospectively followed patients identified by NBS showed mild decline of kidney function (n=3 CKD stage 2; n=10 intermittent CKD stage 2-3a) independently from biochemical subtype or treatment quality starting in school age to adolescence and adulthood [5]. Clinical relevance is unclear and according to the literature and experience of the GDG, none of the patients underwent dialysis. Moreover, acute renal failure has been described in single patients, including a case of lethal atypical haemolytic uraemic syndrome [192-194]. Pathomechanistic studies revealed strong GCDH expression [195], and interference of GA and 3-OH-GA with organic anion transporters in proximal renal tubule cells [196], as well as acute nephrotoxic effects induced my metabolic crisis but also chronic nephrotoxic effects in animal models [50,51].

	Recommendation #19 [new 2022; strong consensus]
Level of recommendation: **B**	Renal function should be assessed yearly starting from age 6 years (**Tab. 7**).

Recommendation	
Level of evidence	Moderate to high (SIGN level 2++ to 4). Consistency of evidence is moderate to high.
Clinical relevance	Moderate.

Additional laboratory monitoring: Basic laboratory and nutritional parameters (**Tab. 7**) may be helpful for detecting insufficient intake of micronutrients or energy substrates [90,123], but are usually normal during the first six years of life in patients receiving adequate maintenance treatment [52]. Therefore, it is sufficient to analyse these parameters only in case of clinical indication or deviations from maintenance treatment recommendations.

Tab. 7 summarises recommendations for routine laboratory monitoring.

Biochemical monitoring during acute illness

Patients are at increased risk for developing acute encephalopathic crisis during episodes of fever, recurrent vomiting, diarrhoea and/or reduced intake of nutrients and fluids, possibly resulting in dehydration, imbalance of electrolytes and metabolic acidosis which should be assessed and recognised on admission followed by adjusted emergency treatment (see **Tab. 5**) aiming at timely metabolic compensation [24,30,35,37,55,66]. CK concentration should be monitored in case of severe MD/status dystonicus and/or signs of rhabdomyolysis [197].

Neuroradiological monitoring

Clinical monitoring after head trauma: GA1 is associated with increased risk of developing traumatic or incidental SDH (see diagnostics, subdural haemorrhage and arachnoid cysts). SDH may occur even under recommended treatment and without macrocephaly [198]. Exact frequency of SDH after head trauma in GA1 has not been studied. A recent study including eight patients with SDH demonstrated that (1) manifestation of SDH peaks at age 10-14 months, but does not occur after age 36 months, (2) has only been observed in HE patients, but, (3) individuals with incidental SDH mostly remain asymptomatic and (4) rarely show 'absolute' but rather 'relative' macrocephaly, i.e. widened external CSF spaces and disproportion of cranial cavity versus brain tissue resulting in widened arachnoid spaces, which declines with age [28]. Therefore, even after minimal or mild head trauma, patients should be closely monitored in an inpatient setting. Of note, planned clinical observation in such individuals has been shown to reduce the use of neuroradiological imaging[199].

	Recommendation #20 [modified 2022; consensus]
Level of recommendation: **B** **Recommendation**	Patients should be admitted to a hospital and closely monitored for at least 24 h even after minimal or mild head trauma within the first three years of life due to the increased risk for developing SDH.
Level of evidence	Moderate to high (SIGN level 1- to 4). Consistency of evidence is moderate.
Clinical relevance	Moderate to high. Effect of inpatient clinical monitoring has not been

	systematically investigated but is supported by the clinical experience of the GDG.

Detection/monitoring of striatal and extrastriatal CNS abnormalities: GA1 patients show characteristic patterns of striatal and extrastriatal MRI abnormalities (**Suppl. Tab. 3, Fig. 1, recommendation #2**).

Striatal abnormalities: Striatal abnormalities, particularly in the putamen, have a high clinical relevance and are strongly associated with dystonic MD [97,99]. *Acute-onset* (median age 270 days, range 147–570)*, insidious-onset* (median age 630 days, range 180–1,680 days) and *acute-on-insidious onset* MD mostly manifest clinically within the first three years of life and can be distinguished neuroradiologically by different striatal patterns. However, single *insidious-onset* patients may show a latency phase of several years between MRI and clinical manifestation [41]. Since development of MD may not be prevented therapeutically after striatal injury has already occurred, there is no evidence for the necessity of serial MRI scans *without* clinical indication during the phase of striatal vulnerability, i.e. the first six years of life. However, MRI imaging should always be performed in all age groups in case of (new) clinical signs of MD, SDH or other new or significantly aggravated neurologic symptoms.

Brain MRI including diffusion-weighted imaging detects striatal lesions earlier and more precisely than computer tomography [39,57,65,95,97,108,190,200-204]. Frontotemporal hypoplasia can also be detected by cranial ultrasound [205], even prenatally during last trimester of pregnancy [206,207]

Minimum technical criteria for MRI scans comprise age-adapted sequences, axial T2-, FLAIR and T1-weighted sequences, diffusion-weighted sequence with ADC maps, and, if applicable, 3D-sequence for detection of small subependymal nodules.

	Recommendation #21 [modified 2022; strong consensus]
Level of recommendation: **B Recommendation**	Neuroradiological examination should be performed in all age groups if neurological symptoms occur or deteriorate significantly.
Level of evidence	Moderate (SIGN level 2+ to 4). Consistency of evidence is moderate.
Clinical relevance	High.

Extrastriatal abnormalities: Extrastriatal abnormalities in GA1 occur frequently, are inter-individually variable and dynamic with age [98]. Presumably caused by chronic neurotoxicity their clinical relevance remains unknown [25]. Compared to LE, HE patients show progredient extrastriatal abnormalities and increased concentrations of GA and 3-OH-GA with age detected *in vivo* by ^{1}H-MRS [26]. Late diagnosed *(late-onset)* patients characteristically show frontotemporal hypoplasia and subependymal nodules at the ventricular roof starting from age twelve years with slow progression, so far without histopathological investigation [25,48,58], and also reported in single early treated patients identified by NBS [25,208]. Furthermore, three cases of malignant brain tumours (medulloblastoma, glioblastoma) in individuals not receiving guideline-according maintenance treatment have been published. However, causal association with GA1 remains unclear [59]. A recent retrospective French study revealed thickening of the chiasma opticum in six of ten patients [209].

Serial MRI scans may prove effectiveness of metabolic treatment, i.e., normalization of extrastriatal abnormalities such as frontotemporal hypoplasia as a correlate of effective reduction of neurotoxicity [98,210], but do not have an immediate clinical impact. However, progredient subependymal mass lesions may potentially develop clinical relevance due to the theoretical risk of CSF circulatory dysfunction and malignancy.

	Recommendation #22 [new 2022; strong consensus]
Level of recommendation: **0 Recommendation for research**	Routine MRI investigations for detection and/or monitoring of extrastriatal abnormalities (subependymal noduli, white matter abnormalities) can be started from age ten years and repeated depending on results, e.g. every 2-5 years).
Level of evidence	Moderate (SIGN level 2+ to 3). Consistency of evidence is high.
Clinical relevance	Moderate.

Monitoring of specific neurologic functions

Polyneuropathy: So far, polyneuropathy was only reported in two adult *late-onset* patients [25,48], but systematic studies on prevalence in early or lately treated patients do not exist.

Hearing function: A recent Taiwanese study with 13 patients, with methodical limitations however, reported on mild hearing impairment, particularly in patients after intensive care treatment [211]. It is unknown whether early or late treated individuals with GA1 are generally at increased risk for developing hearing impairment.

Developmental diagnostics of motoric and psychologic functions

Chronic neurotoxicity and frequent structural abnormalities (**Suppl. Tab. 3**) may influence cognitive functions. Thirty years ago, it was assumed that the intellect is 'spared' in GA1 [11] which was confirmed in small case series without control groups using differing methodologies [53,65,212]. A Taiwanese study reported on nine children identified by NBS with normal cognitive functions [56]. Another study with 30 patients using computer-based test battery for information processing showed similar neuropsychological functions in asymptomatic patients compared to a healthy control group, whereas dystonia primarily influenced performance in tests measuring motor speed but not tests with higher cognitive demand [166]. A recent US study reported on normal psychomotor development in 60 patients identified by NBS and normal cognitive functions in ten of them [34].

In contrast, IQ and cognitive dysfunction may also be impaired in early and late treated children [213-215]. Cognitive performance of 72 prospectively followed individuals identified by NBS in Germany was lower than average range (mean IQ of 87) and impacted by biochemical subtype with LE patients showing normal cognitive performance (mean IQ 98) while HE patients had significantly lower results (mean IQ 84), independent of treatment quality or motor phenotype [29]. There are also case reports on cognitive decline and dementia in late diagnosed patient [25,44].

Standardised monitoring of psychologic functions should include intelligence (developmental quotient in younger children), motor functions (including fine motor skills), and language (**Tab. 6**) and, in case of detection of specific deficits, enables start of supportive treatment intervention, such as occupational, speech or psycho-

therapy. Since cognitive studies only included a small number of patients with severe MD, adjusted test instruments are recommended for these patients (**Tab. 6**).

	Recommendation #23 [modified 2022; strong consensus]
Level of recommendation: **B** **Recommendation**	Intelligence/developmental quotient, motor functions and language should be evaluated regularly to detect specific deficits and allow start of supportive treatment. For severely affected patients adjusted test batteries should be used (**Tab. 6**).
Level of evidence	Moderate to high (SIGN level 2++ to 3). Consistency of evidence is moderate.
Clinical relevance	High.

Quality of life

Since metabolic diseases treated with diet have a huge influence on average-day life, assessment of psychosocial factors and quality of life in affected individuals and families is an important part of long-term management [216-218]. Individuals with organic acidurias show more behavioural and emotional problems, and impact of the disease may be a greater burden on the family than on the patient [219]. Therefore, psychosocial effects and quality of life should be regularly assessed in affected patients and their families (see **recommendation #14**).

Medical health care procedure

No systematic studies are available to determine optimal health care management of GA1. Based on the best clinical experience the GDG recommends the following procedure:

After confirmation of diagnosis (**Fig. 1**), the patient is admitted to an interdisciplinary centre experienced in managing metabolic diseases for a short-period inpatient stay. Maintenance treatment is initiated (**Tab. 2**), and parents are theoretically and practically educated in the importance of metabolic maintenance and emergency treatment and recognising symptoms that indicate impending catabolism Psychosocial advice, emergency cards including optimizing strategies (**Tab. 3,4**) and contact information of the metabolic centre are provided. Frequency and content of regular follow-up investigations are explained. Use of interpreters may be required. Long-term management requires close cooperation of the metabolic centre with local hospitals (e.g., for emergency treatment), local general paediatricians (e.g., vaccinations, regular medical check-ups), specialised outpatient departments, family support groups (exchange of experience), and other facilities, such as schools, kindergartens and day-care centres. Moreover, translation of new research findings into clinical management is of huge importance.

Transition to adult medicine and long-term care

In analogy to other metabolic disease adult patients with GA1 should be followed by adult physicians experienced in managing metabolic diseases aiming at (1) maintaining and monitoring general treatment compliance, (2) detection of disease-specific long-term complications and (3) managing of adult-specific medical issues (e.g., metabolic syndrome, diseases of musculoskeletal system, fertility, family planning).Transition should be broached early (e.g., starting at age 14 years) and organised as a continuous and

interdisciplinary process. In Germany, Austria, and Switzerland transitional care concepts for rare diseases are increasingly being developed in which adult internal specialists initially see affected individuals together with the paediatric treatment team, and later on independently [220]. If supervision by adult specialists is not possible, follow-up should be continued by the paediatric metabolic centre.

In chronic diseases problems with compliance in puberty and early adulthood may negatively impact outcome [221]. As long-term course of metabolic diseases is still unknown, continuous supervision by a metabolic is essential.

	Recommendation #24 [new 2022; strong consensus]
Level of recommendation: **B Recommendation**	Starting from age 14 years and depending on local health care structures, transition (interdisciplinary paediatric-internal consultation) followed by transfer to adult medicine should be broached and organised as a structured and standardised procedure.
Level of evidence	Low (SIGN level 3). Consistency of evidence is moderate.
Clinical relevance	High.

Although several aspects of neuropathogenesis, phenotypic spectrum and clinical long-term course are still unclear, knowledge on GA1 has continuously increased since the first publication of the guideline 15 years ago [3]. Following the first two revisions of the guideline [1,2] treatment concepts have further been optimised and implemented into clinical practice. Early timepoint of diagnosis facilitated by NBS and continuous adherence to maintenance and emergency treatment recommendations have led to significantly improved outcome. For this third revision of proposed recommendations new recent research findings, such as increasing evidence for the impact of treatment quality on outcome, evolving phenotypic diversity and variant disease courses, long-term outcome, neuroradiological and extraneurological manifestations as well as the perspective of affected individuals have been implemented, and hopefully will be accepted and practiced.

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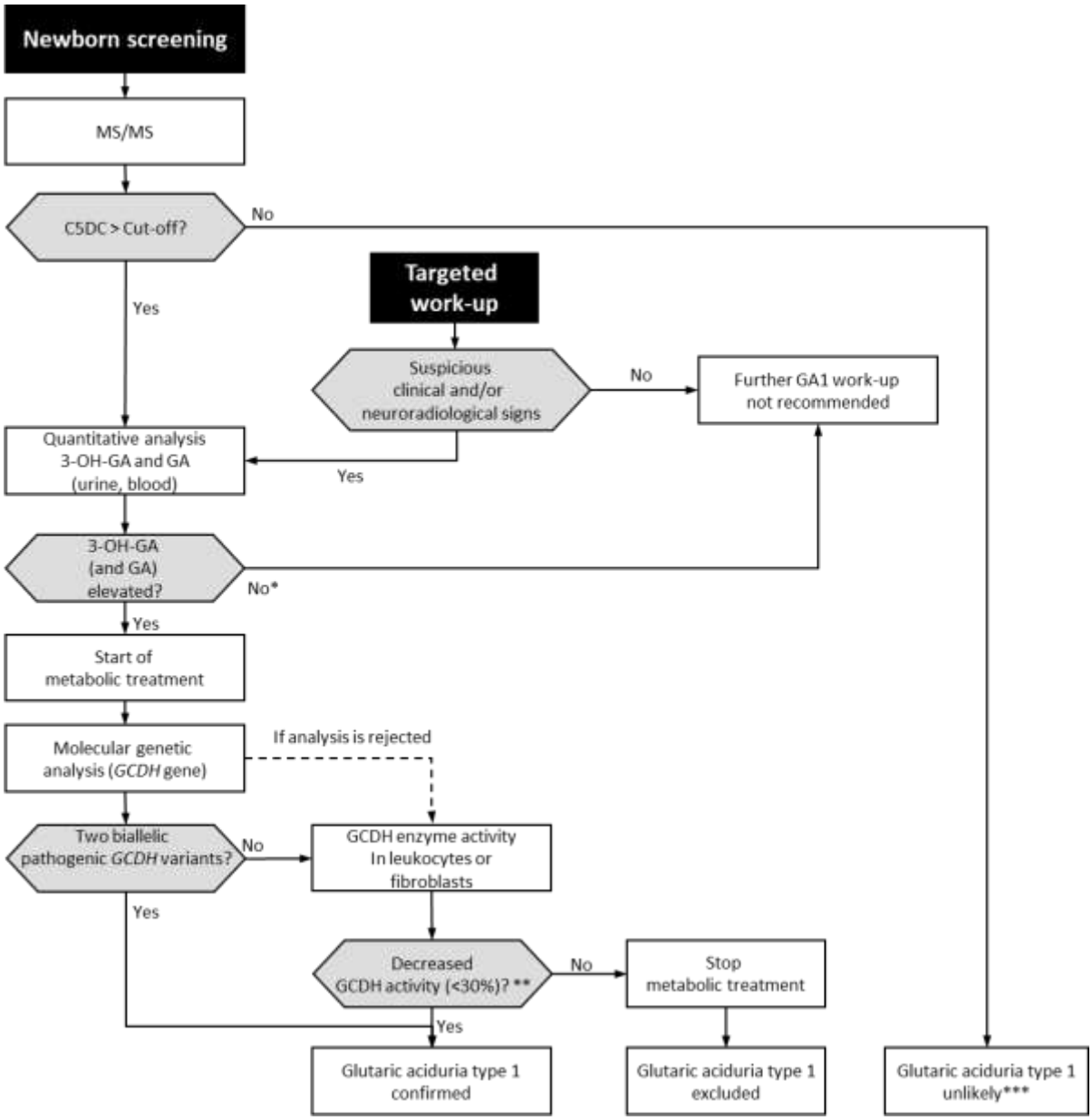

Fig 1. Algorithm for diagnostic work-up in GA1

Newborn screening is performed using MS/MS analysing C5DC concentration in DBS. Diagnostic confirmation of abnormal NBS results includes quantitative analysis of GA and 3-OH-GA in urine and/or blood, molecular genetic analysis of *GCDH* gene and GCDH enzyme analysis.

Targeted diagnostic work-up due to suggestive clinical, biochemical and/or neuroradiological signs starts with quantitative analysis of GA and 3-OH-GA in urine and/or blood and is performed in analogy to the described diagnostic work-up procedure.

(*) Low excretors may show (intermittently) normal concentrations of 3-OH-GA (and GA) in urine or blood. In case of highly suggestive signs for GA1, further diagnostic work-up should be considered on an individual basis. Since there is no dietary stratification depending on the biochemical subtype, all individuals receive the same metabolic treatment.

(**) Low excretors show a GCDH residual activity of 3-30% while it is 0-2% in high excretors.

(***) if individuals in this group develop suggestive clinical signs, further work-up according to targeted diagnostic work-up is recommended.

Comment on molecular genetic and enzyme analysis: Due to (1) broader availability of *GCDH* gene analysis compared to GCDH enzyme analysis, and (2) importance of molecular genetic analysis for both disease confirmation and accurate genetic counselling and prenatal diagnosis, start with genetic testing for confirmation is recommended. However, initial GCDH enzyme analysis may be suitable depending on local availability, experience and the patient's and his family's preference.

Table 1. Summary of all 24 recommendations.

#	Diagnostic procedures	Level of recommendation*
1	When GA1 is suspected, (differential-) diagnostic work-up, development of treatment plans, appropriate education and training of affected individuals and their families should take place in a specialised centre experienced in managing inherited metabolic diseases. Affected individuals diagnosed elsewhere should be transferred to such centres without delay.	Strong recommendation for (A)
2	Positive (abnormal) NBS results and/or suggestive clinical, biochemical and/or neuroradiological signs should be confirmed by diagnostic work-up, including quantitative analysis of GA and 3-OH-GA in urine and/or blood, and, if abnormal, molecular genetic analysis of *GCDH* gene and/or GCDH enzyme analysis in leukocytes or fibroblasts (**Fig. 1**).	Strong recommendation for (A)
3	In children with SDH/hygroma (fluid collections) in combination with further characteristic neuroradiologic signs (frontotemporal hypoplasia with widening of anterior temporal CSF spaces and the Sylvian fissure, **Supp. Tab. 2**), targeted diagnostic work-up (using the algorithm in **Fig. 1**) is **s**trongly recommended.	Strong recommendation for (A)
4	In children with a positive (abnormal) NBS result, but negative (normal) confirmatiory diagnostic work-up, the mother may be informed about the possible condition of a maternal GA1 which can be further examined by targeted diagnostic work-up (**Fig. 1**).	Recommendation for research (0)
	Metabolic maintenance treatment	
5	Metabolic maintenance treatment should be implemented and regularly evaluated by an interdisciplinary team in a specialised centre experienced in managing inherited metabolic diseases.	Strong recommendation for (A)
6	A low lysine diet is strongly recommended in all patients up to the age of six years. To ensure sufficient protein intake, additional administration of lysine-free, tryptophan-reduced and arginine-enriched amino acid mixtures is strongly recommended.	Strong recommendation for (A)
7	After age six years, dietary treatment should follow an age-adapted, protein-controlled protocol which is based on safe levels for protein intake and avoids excessive intake of food with high lysine content. Dietary transition should be accompanied by regular dietary advice.	Recommendation for (B)
8	Since there is no evidence for clinical benefit of the use of arginine as a single amino acid for maintenance or emergency treatment in addition to arginine intake via natural food and AAM, an additional arginine supplementation is not recommended.	Recommendation for research (0)
9	Carnitine should be supplemented lifelong aiming to maintain the concentration of free carnitine in plasma or dried blood spots within the reference range.	Recommendation for (B)

Metabolic emergency treatment		
10	It is strongly recommended to start emergency treatment immediately and to perform it aggressively in any case of febrile illness, , or alarming symptoms as well as during perioperative management within the vulnerable period for striatal injury (up to age six years).	Strong recommendation for (A)
11	Emergency treatment after age six years can be administered during episodes of severe illness or perioperative management in analogy to the age group 0-6 years with individual adaptation of glucose and fluid intake.	Recommendation for research (0)
Neurologic complications		
12	Diagnosis and therapy of neurologic (i.e., movement disorder, symptomatic epileptic seizures) or neurosurgically treatable manifestations (SDH) should be managed by a neuropaediatrician/neurologist and/or neurosurgeon in close cooperation with metabolic specialists.	Strong recommendation for (A)
Vaccinations		
13	All patients with GA1 should be vaccinated according to national recommendations.	Recommendation for (B)
Disease education		
14	Age-specific education and information of affected patients and their families on disease course, treatment and prognosis as well as socio-legal advice and evaluation of quality of life should be regularly provided by an interdisciplinary team including experts in metabolic medicine, nutritional therapy, physiotherapy, social-advice and psychology.	Recommendation for (B)
Clinical monitoring		
15	Therapeutic effectiveness and adverse side effects should be monitored by regular follow-up investigations and intensified in case of symptom progress or non-adherence to treatment recommendations. For recommended endpoints of clinical monitoring see recommendations **#17-20, 23, 24** and **Tab. 6**.	Strong recommendation for (A)
16	Analysis of urinary concentrations of GA and 3-OH-GA should not be used for monitoring or adaption of treatment.	Recommendation for (B)
17	Concentrations of plasma amino acids should be regularly quantified in patients with low lysine diet (3-4 hrs postprandially) and be maintained within the age-specific normal range (**Tab. 5**).	Strong recommendation for (A)
18	Concentration of free carnitine in plasma or dried blood spots should be monitored regularly in all individuals with GA1. Trough level concentration of free carnitine (at least 12 hours after last administration) should be maintained within the reference range.	Recommendation for (B)
19	Renal function should be assessed yearly starting from age 6 years (**Tab. 7**).	Recommendation

		for (B)
20	Patients should be admitted to a hospital and closely monitored for at least 24 h even after minimal or mild head trauma within the first three years of life due to the increased risk for developing SDH.	Recommendation for (B)
21	Neuroradiological examination should be performed in all age groups if neurological symptoms occur or deteriorate significantly.	Recommendation for (B)
22	Routine MRI investigations for detection and/or monitoring of extrastriatal abnormalities (subependymal noduli, white matter abnormalities) can be started from age ten years and repeated depending on results, e.g. every 2-5 years).	Recommendation for research (0)
23	Intelligence/developmental quotient, motor functions and language should be evaluated regularly to detect specific deficits and allow start of supportive treatment. For severely affected patients adjusted test batteries should be used (**Tab. 6**).	Recommendation for (B)
Transition		
24	Starting from age 14 years and depending on local health care structures, transition (interdisciplinary paediatric-internal consultation) followed by transfer to adult medicine should be broached and organised as a structured and standardised procedure.	Recommendation for (B)

*Level of recommendation according to [63,222].

Table 2. Metabolic maintenance treatment

Treatment		Age				
		0–6 months	**7–12 months**	**1–3 years**	**4–6 years**	**> 6 years**
1. Low lysine diet						
Lysine (from natural protein)[a]	*mg/kg per day*	100	90	80-60	60-50	Controlled protein intake using natural protein with a low lysine content and avoiding lysine-rich food; e.g. according to national recommendations like 'Optimix'[e]
AAM (synthetic protein)[b]	*g/kg per day*	1.3-0.8	1.0-0.8	0.8	0.8	
Energy[c]	*kcal/kg per day*	100-80	80	94-81	86-63	
2. Micronutrients[c]	%	≥ 100	≥ 100	≥ 100	≥ 100	≥ 100
3. Carnitine[d]	mg/kg per day	100	100	100	100-50	50-30

[a]Lysine/protein ratios vary considerably in natural food and thus natural protein intake in children on a low lysine diet is dependent on the natural protein source. The natural protein intake is relatively high if patients predominantly use natural protein with a low lysine content. For this reason, numerical data on natural protein are not provided.

[b]Lysine-free, tryptophan-reduced, arginine-fortified AAM should be supplemented with minerals and micronutrients as required to maintain normal levels. Adequate intake of essential amino acids is provided from natural protein and AAM supplements. Amount of AAM is adjusted to reach at least the 'safe levels' [121].

[c]According to international dietary recommendations [223]. Recent updates on recommendations for energy intake [224] do not refer to body weight anymore.

[d]Carnitine dosage may be adapted to maintain the concentration of free carnitine within the reference range.

[e]Optimix®, National nutritional recommendations for children and adolescents, by *Research Department for Child Nutrition, Bochum, Germany*; URL: https://www.fke-shop.de/das-neue-fke/

Treatment should be modified according to individual needs in case of growth and development disturbances.

AAM, amino acid mixtures

Table 3. Strategies to optimise emergency treatment

Target topic	Proposed strategy
Education and training of parents	Parents should be informed in detail about natural history, maintenance and emergency treatment, prognosis and the particular risk for the manifestation of an acute encephalopathic crisis. Education should be performed regularly by the responsible metabolic centre.
Treatment protocols / Emergency cards	Written protocols for maintenance and emergency treatment should be regularly updated and provided to all persons involved (parents, metabolic centres, local hospitals and paediatricians). Also, an emergency card (preferably laminated) should be provided summarising key information and principles of emergency treatment and containing contact information of the metabolic centre.
Supplies	Adequate supplies of specialised dietetic products (maltodextrin, lysine-free, tryptophan-reduced amino acid mixtures) and medication required for maintenance and emergency treatment (carnitine, antipyretics) should always be maintained at home.
Close cooperation with local hospitals and paediatricians	After new diagnosis of GA1 in a child, the closest hospital and local paediatrician should be informed and instructed. Essential information including written treatment protocols should be provided *before* inpatient emergency treatment might be necessary. Inpatient emergency treatment can take place in the closest hospital if the responsible metabolic centre is far away. The responsible metabolic centre should be contacted for supervision without delay.
Holiday management	Those metabolic specialists/centres closest to the holiday resort should receive information about GA1 and the recent treatment *before* start of the vacation. Parents should be provided with contact information of the corresponding specialist.
Consultation of metabolic centre at infectious diseases	Parents or local hospitals/paediatricians should immediately inform the responsible metabolic centre if (1) temperature rises over 38.5 °C, (2) vomiting/diarrhoea or other symptoms of intercurrent illness develop, or (3) new neurologic symptoms occur. Management of emergency treatment should always be supervised by the responsible metabolic centre.
Perioperative management	If an elective surgical intervention is planned, the responsible metabolic centre should be informed *in advance* to discuss with surgeons and anaesthesiologists. In case of emergency surgical intervention, the responsible metabolic centre should be informed without delay to supervise perioperative management-

Table 4. Outpatient emergency treatment (up to age six years)

A. Oral carbohydrates[a]	**Maltodextrin**			
Age (years)	%*	kcal/100 mL	KJ/100 mL	Volume (mL) per day orally
Up to 0.5	10	40	167	min. 150 ml/kg
0.5-1	12	48	202	120 ml/kg
1-2	15	60	250	100 ml/kg
2-6	20	80	334	1200-1500 ml
B. Protein intake				
Natural protein	According to emergency dietary plan. 50% reduction or stop for maximum of 24 hours, then reintroduce and increase stepwise until the amount of maintenance treatment plan is reached within 48 -72 hours.			
AAM	AAM should be administered according to maintenance treatment, if tolerated (**Tab. 2**).			
C. Pharmacotherapy				
Carnitine	Double carnitine intake: e.g., 200 mg/kg/d p.o. in infants.			
Antipyretics	If body temperature rises above 38.5 °C (101 F), antipyretics, such as ibuprofen or paracetamol (each 10-15 mg/kg per single dose, 3-4 doses daily, maximum daily dose 60 mg/kg) should be administered.			

[a]Maltodextrin solutions [159] should be administered every 2 hours day and night. Concentrations may be adapted if clinically indicated. If AAM is tolerated it may be fortified with maltodextrin. Individuals should be reassessed every 2 hours for level of consciousness, feed tolerance, fever and alarming symptoms.

*Referring to volume percent, i.e., 100 g maltodextrin in 1000 ml water result in a 10% solution.

AAM, lysine-free, tryptophan-reduced, arginine fortified amino acid mixtures.

Table 5. Inpatient emergency treatment (up to age six years)

A. Intravenous infusions		
Glucose	Age (years)	Glucose (g/kg per day IV)[a]
	0-1	(12-) 15
	1-3	(10-) 12
	3-6	(8-) 10
Insulin	If persistent hyperglycaemia >150-180 mg/dL (>8-10 mmol/L) and/or glucosuria occurs, start with 0.025-0.05 IU insulin/kg/h IV and adjust the infusion rate according to serum glucose (aim: normoglycemia).	
B. Protein intake		
Natural protein	Stop for 24 (max. 48) hours, then reintroduce and increase stepwise until the amount of maintenance treatment plan is reached within 48 (-72) hours.	
AAM	AAM should be administered according to maintenance treatment, if tolerated, (**Tab. 2**).	
C. Pharmacotherapy		
Carnitine	Carnitine i.v. according to normal daily dose, i.e., 100 mg/kg/d IV in infants (**Tab. 1**).	
Antipyretics	If body temperature rises >38.5 °C (101 F), antipyretics, such as ibuprofen or paracetamol (each 10-15 mg/kg per single dose, 3-4 doses daily, maximum daily dose 60 mg/kg) should be administered.	
Sodium bicarbonate	In case of acidosis; alkalization of urine facilitates urinary excretion of organic acids	
D. Monitoring		
Vital signs	Heart rate, blood pressure, temperature, diuresis; Glasgow Coma Scale if reduced consciousness; assessment for neurologic signs (hypotonia, irritability, rigor, dystonia)	
Metabolic parameters	Blood: glucose, blood gases, creatine kinase, amino acids (plasma)[b], carnitine (plasma or dried blood spots) Urine: ketone bodies, pH	
Routine laboratory	Electrolytes, blood count, creatinine, C-reactive protein, blood culture (if indicated)	

[a] mg/kg/min*1.44=g/kg/per day

[b]During the recovery phase.

AAM, amino acid mixtures.

Table 6. Clinical monitoring

		Frequency at age			
Domain	**Clinical endpoints**	**0-1 year**	**1-6 years**	**> 6 years**	**> 18 years**
History	General history and development, intercurrent infections, outpatient or inpatient emergency treatment, dietary treatment, pharmacotherapy, vaccinations, regular paediatric preventive examinations	Every 3 months	Every 6 months	1/year	1/year
Anthropometrics	Body weight, body length, head circumference	Every 3 months	Every 6 months	1/year	1/year
Clinical status	General examination, developmental milestones, neurologic status including fine motor skills, evaluation of MD like dystonia, chorea, tremor, muscle weakness, speech articulation and reception, behavior, concentration, development	Every 3 months	Every 6 months	1/year	1/year
Nutrition therapy	Daily lysine intake (mg/kg/d), daily intake of natural protein and protein from AAM (g/kg/d), calories (kcal/kg/d), fat intake (g/kg/d)	Every 3 months	Every 6 months	1/year	1/year
Laboratory parameters	See **Tab. 7**	Every 3 months	Every 6 months	1/year	1/year
Neuroradiology	cMRI (see **recommendation #21**)	At any neurologic deterioration			
	Detection/ follow up of extrastriatal abnormalities (see **recommendation #22**)				If applicable from age 10 years, every 2-5 years
Developmental parameters of motor and psychologic functions	Regular evaluation of intelligence, motor function and speech/language (see **recommendation #23**)		at 12 and 24 months: *BSID-III /Denver-Scales* at 3 years: *WPPSI-III/IV* at 5 years: *WPPSI-III/IV*	at 8 years: *WISC-V*	at 18 years: *WAIS-IV*
			Patients with (severe) MD: *Raven's Progressive Matrices 2, 2019* (if cognitive functions allow participation) *Vineland Adaptive Behavior Scales - Third Edition, 2021* (if cognitive functions do not allow participation)		
Quality of life	Separate assessment of quality of life for affected individuals and their parents		1/year		
Psychosocial counselling	Reimbursement of expenses for medication or travel, handicapped ID, etc.	At initial presentation	On request		
Genetic counselling	Basic genetic information, examination of further family members, family planning, prenatal diagnostics, etc.	At diagnosis and on request during follow up (i.e., in context of transition).			

BSID-III: Bayley Scales of Infant and Toddler Development - Third Edition 2006; *cMRI:* cerebral magnetic resonance imaging; *MD:* movement disorder*; WAIS-IV:* Wechsler Adult Intelligence Scale - Fourth Edition, 2012;

WISC-V: Wechsler Intelligence Scale for Children - Fifth Edition, 2017; *WPPSI-III:* Wechsler Preschool and Primary Scale of Intelligence - Third Edition 2006; *WPPSI-IV:* Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition 2018.

Table 7. Routine laboratory monitoring

		Frequency at age			
Parameter	**Rationale**	**0-1 years**	**1-6 years**	**> 6 years**	**> 18 years**
Amino acids (plasma)	General nutritional status	Every 3 months	Every 6 months	Every 12 months	Every 12 months
Carnitine status (plasma, serum or DBS)	Secondary carnitine depletion, compliance	Every 3 months	Every 6 months	Every 12 months	Every 12 months
Creatinine, cystatin C, GFR If applicable, spot urine	Kidney function [b]	-	-	Every 12 months	Every 12 months
Complete blood count, calcium, phosphorous, albumin, liver enzymes, parathormone, ferritin, vitamin B12, alkaline phosphatase, CK	General nutritional and metabolic status, bone metabolism[a]	Only at clinical abnormalities, i.e., signs for malnutrition, failure to thrive, feeding problems or signs of deviations from maintenance treatment recommendations. CK only in case of severe dystonia/status dystonicus and/or new clinical symptoms (pain/weakness) or signs of rhabdomyolysis.			

[a]If abnormal bone mineralisation is suspected, additional tests are required (e.g., radiological investigations for bone age and density).

[b] Kidney function (GFR) can be measured in blood by measuring creatinine or cystatin C (calculation of GFR according to Schwartz formula). In dystrophic patients, creatinine concentration may be reduced. Screening analyses in spot urine allow differentiation between tubular and glomerular nephropathy (protein-to-creatinine-ratio, α1/β2-microglobuline). Time-consuming analysis in 24h urine depends on methodically correct specimen and therefore is *per* se not justified.

CK, creatine kinase; *DBS*, dried blood spots; *GFR,* glomerular filtration rate