Neurocognitive outcome and mental health in children with tyrosinemia type 1 and phenylketonuria: A comparison between two genetic disorders affecting the same metabolic pathway

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Abbreviations: ASEBA, Achenbach System of Empirically-Based Assessment; BH4, tetrahydrobiopterin; BRI, Behavior Regulation Index; CBCL, Children Behavioral Checklist; MI, metacognitive Index; NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione; PKU, phenylketonuria; SSRS, Social Skills Rating System; TT1, tyrosinemia type 1; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scale for Children; YSR, Youth Self Report.

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Abstract

Tyrosinemia type 1 (TT1) and phenylketonuria (PKU) are both inborn errors of phenylalanine-tyrosine metabolism. Neurocognitive and behavioral outcomes have always featured in PKU research but received less attention in TT1 research. This study aimed to investigate and compare neurocognitive, behavioral, and social outcomes of treated TT1 and PKU patients. We included 33 TT1 patients (mean age 11.24 years; 16 male), 31 PKU patients (mean age 10.84; 14 male), and 58 age- and gender-matched healthy controls (mean age 10.82 years; 29 male). IQ (Wechsler-subtests), executive functioning (the Behavioral Rating Inventory of Executive Functioning), mental health (the Achenbach-scales), and social functioning (the Social Skills Rating System) were assessed. Results of TT1 patients, PKU patients, and healthy controls were compared using Kruskal–Wallis tests with post-hoc Mann–Whitney U tests. TT1 patients showed a lower IQ and poorer executive functioning, mental health, and social functioning compared to healthy controls and PKU patients. PKU patients did not differ from healthy controls regarding these outcome measures. Relatively poor outcomes for TT1 patients were particularly evident for verbal IQ, BRIEF dimensions “working memory”, “plan and organize” and “monitor”, ASEBA dimensions “social problems” and “attention problems”, and for the SSRS “assertiveness” scale (all $p$ values <0.001). To conclude, TT1 patients showed cognitive impairments on all domains studied, and appeared to be significantly more affected than PKU patients. More attention should be paid to investigating and monitoring neurocognitive outcome in TT1 and research should focus on explaining the underlying pathophysiological mechanism.

Keywords

Amsterdam Neuropsychological Tasks, executive functions, neurocognitive outcome, phenylketonuria, social cognition, tyrosinemia type 1
1 | INTRODUCTION

Tyrosinemia type 1 (TT1; McKusick 276700) and phenylketonuria (PKU; McKusick 261600) are both inborn errors of metabolism affecting the phenylalanine–tyrosine metabolic pathway and both disorders feature problems in the neurocognitive domain.

TT1, with an incidence of approximately 1:100 000 newborns, is caused by a deficiency of fumarylacetoacetate hydrolase (EC 3.7.1.2), which is located at the end of the phenylalanine–tyrosine catabolic pathway. This deficiency leads to the accumulation of toxic metabolites, causing liver disease with end-stage liver failure, liver cancer, renal tubulopathy, acute porphyric attacks with neuropathy, and cardiomyopathy. In the past, patients often required liver transplantation or died at a young age. Since 1992, treatment includes the drug 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). NTBC prevents the formation of toxic metabolites, but leads to a further increase in tyrosine concentrations, which have been associated with keratitis and neurocognitive impairments. Therefore, in order to lower the tyrosine concentrations, treatment with NTBC needs to be combined with dietary restriction of tyrosine and its precursor phenylalanine. The combination of early diagnosis by newborn screening along with treatment with NTBC and diet has dramatically improved life expectancy in patients with TT1 and prevents death and/or liver problems. In these treated patients, however, neurocognitive problems have been observed.

In contrast, PKU affects approximately 1 in 10 000 newborns. In PKU, the enzyme phenylalanine hydroxylase (EC 1.14.16.1), which normally converts phenylalanine into tyrosine, is deficient. This result in high phenylalanine concentrations in blood and brain, which cause profound intellectual impairment. Early and continuous treatment with a phenylalanine-restricted diet prevents the severe intellectual disability in PKU patients, although some cognitive and social problems remain.

While the current treatment regimens for both TT1 and PKU are very successful in preventing the most severe complications, both diseases are associated with neurocognitive problems. In early treated PKU patients a lower IQ compared to controls has been reported, as well as problems in executive functioning, behavior, and social cognition. In NTBC-treated TT1 patients, evidence is growing that these patients also have neurocognitive and behavioral deficits such as a lower and/or declining IQ, school and attention problems, problems in executive functioning and social cognition, and suboptimal mental health and quality of life. However, a recent paper by Spiekerkoetter et al. on long-term safety in treated TT1 patients demonstrated a normal rate of cognitive and developmental problems, with an incidence of 3%, although this was based on physician’s reported outcome and not measured. Therefore, the authors acknowledged that more clinical research data were necessary. In addition, they suggest some parallels with PKU, but a direct comparison between TT1 and PKU has not been performed yet.

This parallel with PKU patients may be of importance as treatment strategies are similar (with diet and amino acid supplements), both diseases show abnormal blood phenylalanine/tyrosine ratios, and both diseases exhibit suboptimal neurocognitive outcome. Moreover, it has been hypothesized that similar pathophysiological mechanisms may be underlying these deficits in PKU and TT1. High blood concentrations of a specific amino acid (phenylalanine or tyrosine) could potentially inhibit the influx of other amino acids to the brain as all large neutral amino acids are transported across the blood–brain barrier via the L-type amino acid transporter. This may result in an imbalance in brain amino acid concentrations. The resulting high phenylalanine or tyrosine concentrations may also have a direct neurotoxic effect on the brain. Additionally, these abnormal amino acid concentrations may negatively affect neurotransmitter synthesis of dopamine and serotonin in both TT1 and PKU thereby affecting neurocognitive outcome. Because of all this, similarities in neurocognitive performance in TT1 and PKU may suggest similarities in pathophysiological mechanisms underlying these problems. Thereby, comparisons between TT1 and PKU may give more direction to future research and possible treatment targets. To better understand whether these disorders in phenylalanine-tyrosine metabolism have a comparable neurocognitive profile, this study aimed (1) to establish a comprehensive assessment of neurocognitive functioning, mental health, and social functioning in TT1, (2) to compare these aspects between PKU and TT1 children for a better understanding of the neurocognitive-behavioral dysfunction especially in TT1, and (3) to investigate whether neurocognition, behavior, and social functioning were more severely affected in one of the two disorders.

2 | METHODS

2.1 | Participants

This study included TT1 patients, PKU patients, and healthy controls <18 years of age. TT1 patients were included from a total of eight centers in the Netherlands, Belgium, The United Kingdom, and Chile. All TT1...
patients were treated with NTBC and a protein-restricted diet with supplements aiming for an upper tyrosine concentration between 400 and 600 μmol/L as treatment target, depending on the treatment center. Transplanted TT1 patients were excluded from this study. Patients with PKU were included from four centers in the Netherlands. All PKU patients were treated with dietary restriction of phenylalanine. Treatment targets for PKU patients were: for patients <12 years of age phenylalanine between 120 and 360 μmol/L and for patients ≥12 years between 120 and 600 μmol/L. Healthy controls were included, and matched to patients with TT1 or PKU by age, sex, and country of origin. Healthy controls were primarily recruited via friends and/or family of patients as much as possible while some were recruited through advertisement or acquaintances of coworkers of the institute. This study design was in accordance with the current revision of the Helsinki Declaration. The study was approved by the Medical Ethical Committees of the participating centers. All patients and/or parents gave written informed consent to participate.

2.2 | Instruments and measures

IQ scores were estimated using two IQ subtests and questionnaires regarding executive functioning, mental health, and social skills were filled out.

IQ was assessed using the Wechsler Intelligence Scale for Children Third and Fourth Edition (WISC) for patients from 7 to 16 years old or the Wechsler Adult Intelligence Scale Third Edition (WAIS) for patients older than 16 years. For both the WISC and the WAIS two tasks were used for estimating IQ: a subtest regarding perceptual reasoning (Block Design) and a test for vocal comprehension (Vocabulary). The IQ tests were administered by either a trained investigator or a psychologist.

The questionnaires used in this study were the Behavior Rating Inventory of Executive Functioning (BRIEF), the Achenbach System of Empirically-Based Assessment (ASEBA), and the Social Skills Rating System (SSRS) for children. All questionnaires were validated and available in Dutch, English, Spanish, or French. Only the SSRS was unavailable in Spanish, therefore, this questionnaire was not filled out by the Chilean participants.

The BRIEF questionnaire investigates executive functioning problems that participants may experience in daily life. The BRIEF questionnaire was filled out by parents. It consisted of eight subscales, two composite scales, namely the Behavior Regulation Index (BRI), the Metacognitive Index (MI), and a total score. The ASEBA questionnaire investigates emotional and behavioral problems as measure for mental health. Adolescents aged 12–18 filled out the Youth Self Report (YSR), and parents of children <12 years, filled out the Children Behavioral Checklist (CBCL). The ASEBA questionnaires consisted of eight subscales, and two composite scales for “internalizing behavior” and “externalizing behavior”. For the BRIEF and the ASEBA questionnaires, T-scores were calculated to correct for age and gender. The SSRS questionnaire measures social skills and behavior and was filled out by parents. This questionnaire consisted of four subscales and a total score. The different subscales and composite scales are shown in Table S1.

2.3 | Statistics

Results of TT1 patients, PKU patients, and healthy controls were compared using Kruskal–Wallis tests. Post-hoc Mann–Whitney U tests were performed and afterward Benjamini–Hochberg correction for multiple analyses/comparisons was applied using a false discovery rate (Q) of 5%. Additional Mann–Whitney U tests were performed to investigate differences between presymptomatically and symptomatically diagnosed TT1 patients, between TT1 patients who were currently receiving, or had at one point received phenylalanine supplementation and TT1 patients without phenylalanine supplementation, between BH4 and non-BH4-treated PKU patients, and between Dutch and non-Dutch healthy controls (Supplementary Materials S2). For these analyses, the Benjamini–Hochberg correction for multiple comparisons was applied as well. In all tests, a p-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics 23 (Chicago, IL).

3 | RESULTS

3.1 | Patient characteristics

This study included 33 TT1 patients (mean age 11.24 years, 16 male), 31 PKU patients (mean age 10.84 years, 14 male), and 58 healthy controls (mean age 10.82 years, 29 male).

Descriptive information on the participants is shown in Table 1. For TT1 patients the age at diagnosis varied between the day of birth and 3.2 years. Patients with PKU were all diagnosed by population-based newborn screening. TT1 patients typically received NTBC in dosages of 1 mg/kg/day. Twelve TT1 patients received...
phenylalanine supplementation, continuously or during a short period of time, due to low blood phenylalanine concentrations (concentrations <30 μmol/L). Fifteen PKU patients were treated with tetrahydrobiopterin (BH4) and protein restriction for optimal metabolic control. For PKU patients, lifetime phenylalanine concentrations ranged between 175 and 414 μmol/L (median 277 μmol/L), and testing day concentrations between 130 and 920 μmol/L (median 306 μmol/L). For TT1 patients, lifetime tyrosine concentrations ranged between 259 and 714 μmol/L (median 403 μmol/L), and phenylalanine concentrations between 16 and 109 μmol/L (median 32 μmol/L). Testing day tyrosine concentrations ranged between 241 and 1060 μmol/L (median 572 μmol/L), and phenylalanine concentrations between 19 and 95 μmol/L (median 45 μmol/L).

### 3.2 IQ tasks

Results of the Block Design and Vocabulary tasks are presented in Figure 1. Kruskal–Wallis tests showed differences between the three groups on both the Block Design and the Vocabulary task ($p = 0.002$ and $p < 0.001$).

Post-hoc Mann–Whitney U tests indicated a lower IQ in the TT1 patients compared to healthy controls on the Block Design task ($p = 0.001$). Furthermore, on the Vocabulary task, a lower IQ was observed for TT1 patients compared to PKU patients ($p < 0.001$) and for TT1 patients compared to healthy controls ($p < 0.001$). No significant differences were observed between PKU patients and healthy controls. After correcting for multiple comparisons using Benjamini–Hochberg correction significant results did not change.

| TABLE 1 Patient characteristics |
|----------------------------------|
| TT1 patients ($N = 33$) | PKU patients ($N = 31$) | Healthy controls ($N = 58$) |
| Mean age; Min-max (years) | 11.24; 6.50–17.73 | 10.84; 6.98–16.65 | 10.82; 5.91–17.13 |
| Sex | 17 F, 16 M | 17 F, 14 M | 29 F, 29 M |
| Time of diagnosis (N) | Neonatal screening (13) | Neonatal screening (31) | NA |
| <2 months (4) | 2–6 months (10) | >6 months (6) |
| BH4 treatment | NA | 15 patients | NA |
| Phenylalanine supplementation | 12 patients | NA | NA |
| Country (N) | NL (4) | NL (31) | NL (36) |
| BE (6) | BE (0) | BE (2) |
| UK (17) | UK (0) | UK (14) |
| CH (6) | CH (0) | CH (6) |
| (Parental) nationality | Dutch (3) | Dutch (31) | Dutch (36) |
| Belgian (6) | Belgian (2) | British (3) |
| British (8) | Pakistani (1) | British/Asian (3) |
| Pakistani (3) | Yemeni (1) | British/Indian (1) |
| British/Asian (1) | Chilean (6) | Chilean (6) |
| Yemeni (1) | Unreported (5) | Unreported (6) |

Abbreviations: BE, Belgium; CH, Chile; F, female; M, male; N, number; NA, not applicable; NL, The Netherlands; UK, The United Kingdom.

**Figure 1** IQ subtest results for TT1 patients, PKU patients, and healthy controls. Data are presented with min–max whisker plots. Higher scores indicate better outcome. Statistical differences between the groups after Benjamini–Hochberg correction are depicted as *. Due to missing questions/questionnaires, the number of patients on the scales varied between 32 and 33 for TT1 patients, and between 56 and 57 for healthy controls. Thirty-one PKU patients were included for both scales.
3.3 | Questionnaires

3.3.1 | BRIEF (Executive functioning)

Figure 2 shows the BRIEF results of the TT1 patients, PKU patients, and healthy controls. Higher scores on the BRIEF questionnaire indicate more problems in executive functioning. Kruskal-Wallis analyses showed differences between the three groups on all domains except “emotional control” (p values ranging from p < 0.001 to p = 0.009). No significant differences were observed between PKU patients and healthy controls.

Post-hoc Mann–Whitney tests showed that TT1 patients scored significantly higher (i.e., more poorly) compared to PKU patients on the domains “inhibit” (p = 0.002), “shift” (p < 0.001), “working memory” (p < 0.001), “plan and organize” (p < 0.001), “organization of materials” (p = 0.006), and “monitor” (p < 0.001). Consequently, significant results were observed for the composite scales “BRI” (p = 0.004), “MI” (p < 0.001), and “Total” (p < 0.001). After Benjamini–Hochberg correction the results on the domains “inhibit”, “organization of materials”, and “BRI” were no longer significant.

3.3.2 | ASEBA (Mental health)

The results of the ASEBA questionnaires are shown in Figure 3. Higher scores indicate more emotional and behavioral problems.

Kruskal–Wallis tests showed significant differences between the groups on the domains “withdrawn/depressed” (p = 0.018), “physical complaints” (p = 0.005), “social problems” (p < 0.001), “thought problems” (p = 0.022), “attention problems” (p < 0.001), “delinquent behavior” (p = 0.015), and “aggressive behavior” (p = 0.002). Next to this, differences between the groups exist on the composite domains “internalizing problems” and “externalizing problems” (p = 0.005 and p = 0.003 respectively). No significant differences were observed between PKU patients and healthy controls.

Post-hoc Mann–Whitney tests showed significantly higher scores for TT1 patients compared to PKU patients on the domains “withdrawn/depressed” (p = 0.047), “social problems” (p = 0.004), “thought problems” (p = 0.023), “attention problems” (p < 0.001), and “aggressive behavior” (p = 0.002). Furthermore, TT1 patients had higher scores, indicating more problems, on the composite domains “internalizing behavior” (p = 0.019) and “externalizing behavior” (p = 0.003). After Benjamini–Hochberg correction the result on the domain “withdrawn/depressed” was no longer statistically significant.
Higher ratings were also evident for TT1 patients compared to healthy controls on the domains “withdrawn/depressed” ($p = 0.006$), “physical complaints” ($p = 0.001$), “social problems” ($p < 0.001$), “thought problems” ($p = 0.010$), “attention problems” ($p < 0.001$), “delinquent behavior” ($p = 0.005$), and “aggressive behavior” ($p = 0.002$). In addition, TT1 patients had higher scores on the composite domains “internalizing behavior” ($p = 0.001$) and “externalizing behavior” ($p = 0.002$). Results did not change after Benjamini–Hochberg correction.

### 3.3.3 | SSRS (Social Functioning)

Figure 4 shows the results of the SSRS questionnaire regarding social functioning. Higher scores indicate better social functioning. Kruskal–Wallis analyses revealed differences between the groups on the domains “assertiveness” ($p = 0.001$), “responsibility” ($p = 0.020$), and “total” ($p = 0.016$). No differences were observed between PKU patients and healthy controls.

Post-hoc tests did show that TT1 patients scored significantly lower compared to the PKU patients on the domains “assertiveness” ($p = 0.007$), “responsibility” ($p = 0.041$), and on the “total” score ($p = 0.033$). After Benjamini–Hochberg correction the results on the domain “responsibility” and the “total” score were no longer significant. In addition, TT1 patients had significantly lower results compared to healthy controls on the domains “assertiveness” ($p < 0.001$), “responsibility” ($p = 0.005$), and “total” ($p = 0.004$). After Benjamini–Hochberg correction the results did not change.

### 3.3.4 | Additional analyses

Additionally performed Mann–Whitney U tests showed no clear differences between pre-symptomatically and symptomatically diagnosed TT1 patients. On two
domains symptomatically diagnosed patients appeared less affected, but this was no longer statistically significant after correction, indicating no clear beneficial effect of early diagnosis and treatment in this sample (Supplementary materials S2). Similarly, no clear differences appeared to exist between TT1 patients with and without phenylalanine supplementation, between BH4 and non-BH4 treated PKU patients, and between Dutch and non-Dutch healthy controls (Supplementary materials S2).

4 | DISCUSSION

This study is the first to compare aspects of neurocognitive functioning, mental health, and social functioning between children and adolescents with TT1 and PKU, while also including data from an age and gender-matched group of healthy controls. We demonstrated that TT1 patients <18 years of age experienced more prominent problems than PKU patients of comparable age on almost all domains. In contrast to the recent report of Spiekerkoetter et al., this study confirmed previous findings that TT1 patients have neurocognitive and behavioral deficits also when compared to healthy controls. As opposed to other study cohorts, however, the PKU patients in this cohort did not show significant problems compared to healthy controls, thereby further substantiating the importance of the issues found in TT1 patients.

Before discussing the results in more detail, some limitations need to be addressed. Due to the rarity of the disease, our group of TT1 patients was quite heterogeneous, both in age, nationality, timing of diagnosis, and treatment. Also, our TT1 patients were not geographically matched to our PKU patients, which may have been a source of bias. For instance, resources, follow-up times and methods, availability of treatment and treatment centers, and disease severity may vary considerably between countries. In addition, many TT1 patients treated in the different centers participated, while PKU recruitment may have been more selective, including only Dutch PKU patients, and with only the more motivated families participating. Furthermore, PKU patients were included when matched to TT1 patients based on age and gender only, rather than on severity of the phenylalanine hydroxylase deficiency, which may have resulted in a milder PKU cohort. To enlighten this factor, approximately half of the PKU patients included in this study received BH4 treatment, which implicates milder PKU phenotypes in this study compared to previous publications. A comparison between the BH4-treated (N = 15) and only dietary-treated PKU patients (N = 16), however, revealed only a minor difference between the two groups on the BRIEF domain “monitor”, and no differences in any other domain or questionnaire (data shown in Supplementary materials S2), suggesting that the effect of BH4 in this study is limited.

The TT1 patients have clear impairments compared to healthy controls. On the BRIEF scales for executive functioning, on the ASEBA scales for emotional and behavioral problems (mental health), and on the SSRS scales for social skills TT1 patients scored worse on practically all domains. Secondly, our PKU patients did not show differences compared to healthy controls on any of the investigated domains, which is in contrast with previous studies from our group.

Comparisons between TT1 patients and PKU patients showed that TT1 patients were reported to have significantly more problems on almost all of the executive functioning scales, on several of the mental health scales, and one of the social skills and functioning scales. Executive functioning is considered to be the most prominently affected cognitive domain in PKU patients.
the executive functions inhibition and working memory together with attention have been found to be impaired in PKU patients. It should be noted, however, that these cognitive problems observed in PKU patients were often correlated to metabolic control, i.e., relatively high phenylalanine levels during critical developmental stages or at the time of assessment. As described, the current treatment guidelines recommend keeping phenylalanine levels between 120 and 360 μmol/L < 12 years of age and between 120 and 600 μmol/L ≥ 12 years of age, which should largely prevent cognitive and social problems. The median historical and concurrent phenylalanine levels of the PKU patients in this sample were 277 μmol/L and 306 μmol/L, respectively, which is well within the target range. Therefore, this studied population was quite well treated and this might very well explain the lack of differences between our PKU patients and healthy controls, and, at the same time, provide support for the current treatment regimen for this group of patients.

The data of the present study also underline that the use of rough estimates of cognitive and social problems is problematic for drawing conclusions in this respect. The study by Spiekerkoetter et al., with 315 TT1 patients, was a non-interventional, non-comparative multicenter study and did not collect systematic data on cognitive outcomes in TT1, but rather subjective (physicians reported) data only. Their study reported a very low incidence of neurocognitive and developmental problems. In contrast, our data on neurocognitive and social outcomes, as well as mental health, are comprehensive and systematic, demonstrating that, in line with several other studies, children and adolescents with TT1 show extensive deficits in these domains.

The cognitive, social, and mental health problems in TT1 patients require further research with respect to the details of neurocognitive impairments, and their underlying mechanism(s). In order to achieve this, regular and consistent measurement of metabolic control, as performed in PKU, as well as regular neurocognitive assessment is required. Elevated tyrosine concentrations are considered to be associated with developmental disabilities in tyrosinemia type 2 and 3, while on the other hand phenylalanine supplementation appeared to benefit a TT1 patient's development who exhibited low phenylalanine concentrations. Therefore, in TT1, heightened or highly fluctuating tyrosine levels and lower-than-normal phenylalanine levels are the most important metabolic candidates to underlie poor cognitive, social, and mental health outcomes. Also, NTBC has been hypothesized to play a role in the development of neurocognitive issues, which was not investigated in this study due to lacking data. Further research should therefore focus on comparing these metabolic candidates, as well as NTBC dosages and concentrations, and relate them to neurocognitive outcome measures. Next to this, we recommend that our results are further substantiated by repeating this study in more homogeneous cohorts, for example, only newborn screened/early treated TT1 patients.

To conclude, the cognitive-behavioral phenotype and related pathophysiology have long been focal points for research in PKU. This has led to clear (and relatively strict) treatment recommendations regarding metabolic parameters and also neuropsychological monitoring. TT1 is clearly behind in knowledge on these aspects due to later recognition of this part of the clinical entity and the rarity of the disease. This study shows that TT1 patients are more severely affected in cognitive and social functioning as well as mental health than PKU patients. Therefore, it is imperative to investigate and monitor these outcomes more thoroughly in TT1 patients, and to investigate the underlying pathophysiological mechanisms. Due to the rarity of the disease, studies with sufficient statistical power require international collaboration using standardized methodology to enable investigation of large(r) cohorts.

AUTHOR CONTRIBUTIONS
Kimber van Vliet, Willem G. van Ginkel, and Rianne Jahja were responsible for the acquisition, analysis, and interpretation of the data and for drafting the article. S.C.J. Huijbregts and F.J. van Spronsen were responsible for the conception and design of this study, the acquisition, the analyses, and the interpretation of the data. They were responsible for drafting and revising the article. Anne Daly, Anita MacDonald, Saikat Santra, Corinne De Laet, Philippe J. Goyens, Rosnhi Vara, Yusof Rahman, David Cassiman, Francois Eyskens, Corrie Timmer, Nicky Mumford, Paul Gissen, Jörgen Bierau, Peter M. van Hasselt, Gisela Wilcox, Andrew A. M. Morris, Elisabeth A. Jameson, Alicia de la Parra, Carolina Arias, Maria I. Garcia, Veronica Cornejo, Annet M. Bosch, Carla E. M. Hollak, M. Estela Rubio-Gozalbo, Martijn C. G. J. Brouwers, Floris C. Hofstede, Maaike C. de Vries, Mirian C. H. Janssen, Ans T. van der Ploeg, and Janneke G. Langendonk were responsible for the acquisition, analysis, and interpretation of data and critically revising the article.

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DATA AVAILABILITY STATEMENT
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
The study was approved by the local medical ethical committees of all participating centers. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All tyrosinemia type 1 and phenylketonuria patients and/or their caregivers gave written informed consent for this study.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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