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Overview of European Practices for Management of Tyrosinemia Type 1: Towards European Guidelines

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ABSTRACT

The introduction of nitisinone (NTBC) and newborn screening for Tyrosinemia type 1 (TT1) enabled preemptive treatment of patients, thereby significantly improving outcomes by preventing liver, kidney, and neurological issues. Treatment goals have shifted from emergency treatment to long-term care. To evaluate the risk of developing complications with aging, due to TT1 itself or its treatment, long-term follow-up is essential. In 2014, an overview of TT1 management practices in Europe was published. Within the Metabolic European Reference Network's subnetwork on amino-and-organic acidurias (MetabERN-AOA), we considered it important to give an update on current TT1 management practices in Europe. An online survey study was performed among members of the MetabERN-AOA subnetwork, and participants of a workshop on TT1 at the European Metabolic Group Meeting of Nutricia. Findings were compared to existing data from the aforementioned publication from 2014 and previously published recommendations. Thirty-two centers (16 European countries) completed the survey. Both consistencies and inconsistencies in TT1 management were seen. Inconsistencies were observed in the frequency and methods of follow-up, dosing of NTBC, and target ranges of biochemical markers. Compared to 2014, key differences included an increased number of patients detected by newborn screening, lower NTBC dosing, and a shift from interest in mainly hepatic to hepatic and neurocognitive outcomes. These results align with trends seen in TT1 recommendations over the years. In addition to numerous consistencies, many aspects in TT1 management still differ widely across Europe, suggesting the need for uniform guidance in clinical management beyond existing recommendations.

1 | Introduction

Tyrosinemia type 1 (TT1, OMIM #276700) is a rare inherited metabolic disease of amino acid metabolism that is caused by a defect in the fumarylacetoacetate hydrolase enzyme (FAH). Deficiency of FAH interrupts the tyrosine (Tyr) catabolic pathway and causes subsequent buildup of toxic metabolites such as fumarylacetoacetate and succinylacetone (SA). This results in severe clinical problems including liver failure, hepatocellular carcinoma, renal tubular dysfunction, pancreas dysfunction, acute porphyria attacks, and hyponatremia.[1]

The members of The TT1 MetabERN Professional Collaboration Group are listed in Appendix A.

For many years, dietary restriction of Tyr and its precursor phenylalanine (Phe) was the only available treatment for TT1. Outcome with this Tyr-and-Phe-restricted diet only was poor, resulting in a high mortality of TT1 patients early in life, mostly due to hepatic failure or carcinoma [1]. This changed in 1992 when 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC, nitisinone) was introduced as a new treatment for TT1 [2]. Originally developed as a herbicide, safety testing revealed that NTBC effectively inhibits an enzyme proximal to FAH in the Tyr catabolic pathway, namely 4-hydroxyphenylpyruvate dioxygenase (4HPPD). By this, NTBC prevents downstream accumulation of toxic metabolites like fumarylacetoacetate and SA, and significantly improves clinical outcome in TT1 [2–4].

The benefits of early treatment with NTBC made TT1 a suitable candidate for newborn screening (NBS), which has now been implemented in many countries [5, 6]. Subsequently, preemptive treatment with NTBC resulted in even better prevention of liver disease, renal tubulopathy, and neuropathy and reduced the risk of developing hepatic malignancy to practically zero if treatment is started early and is well maintained [7]. However, NTBC introduced new obstacles [8]. For example, NTBC further increases Tyr concentrations, which can cause ophthalmological (mostly corneal) issues [9, 10], and may require intensifying the Tyr-and-Phe restricted diet, risking hypophenylalaninaemia [2, 11–13]. Moreover, cognitive impairment and brain dysfunction are seen in TT1 patients treated with NTBC, and it is unclear whether these problems result from TT1 or its treatment [14]. These issues highlight that the management and outcome of TT1 may have changed after the introduction of NTBC and NBS, but still offers major challenges [8].

Several groups have summarized the issues in TT1 patients on NTBC treatment in the past [11–13, 15]. One of those is the cross-sectional 2014 study by Mayorandan et al. that investigated clinical practice in TT1 at 21 European centers, giving survey-based recommendations [15]. With the present study, we intend to add further data by providing an up-to-date overview of European practices in the management of TT1, comparing data to those of Mayorandan et al. [15] and assessing alignment of results on management to published recommendations.

2 | Methods

2.1 | Aim 1 (Overview of Current Practices in TT1 Management)

2.1.1 | Survey Creation and Distribution

An online survey study was conducted and performed using Qualtrics, a web-based survey platform (https://www.qualtrics.com/), to obtain an overview of current European practices in the management of TT1. The first draft of the survey was created by AMK and underwent several revisions following feedback from a select group of co-authors (FJvS, AD, AM). The survey contained 60 questions divided into 11 categories related to TT1, namely (1) participant information, (2) center demographics, (3) patient demographics, (4) diagnosis, (5) dietary treatment, (6) treatment with NTBC, (7) metabolic monitoring, (8) hepatic malignancy, (9) neurocognition, (10) pregnancy, and (11) liver transplantation (Appendix S1, A).

The survey was emailed to all health care professionals treating TT1 patients who are affiliated with the subnetwork on amino and organic acidurias of the European Metabolic Reference Network (MetabERN-AOA) and distributed to participants attending the workshop at the European Metabolic Group Meeting of Nutricia on care in TT1 in 2022. The email contained an explanation of the study, privacy regulations, and the link to participate. Informed consent was obtained through the first question. Two reminders were sent 2 and 4 weeks after the initial invitation. Questions were user-adaptive, meaning the number of results per question varied by respondent—for example, responses to questions about child or adult care depended on whether the physician treated children, adults, or both. If not applicable, respondents were allowed to skip certain questions.

2.1.2 | Data Analysis

Only completed surveys from participants who provided full consent were analysed. Descriptive statistics were used exclusively. In case of multiple submissions from the same treatment center, responses were checked for similarity, discrepancies were addressed via personal email, and answers were adjusted accordingly. Furthermore, responses were checked for location, IP address, dates and times of filling in the survey to check for multiple responses from the same participant. Duplicates were removed before analyses. The manuscript was written using the CHERRIES checklist (Appendix S1, B) for reporting results from online questionnaires [16].

2.1.3 | Ethical Statement

This study does not contain any information allowing tracing of individual patients; therefore, ethical approval was not requested.

2.2 | Aim 2 + 3 (Comparison to Data of Mayorandan et al. and Existing Recommendations)

After collecting all data from the survey, a literature search was conducted and two tables were created: one comparing the results of the current study and the data from Mayorandan et al. [15] (Table 1) and one comparing previously published recommendations (Table 2) [11–13, 15, 17].

3 | Results

3.1 | Aim 1: Overview of Current TT1 Management as Evaluated by the Survey

3.1.1 | Responses to the Survey

In total, 33 participants completed the survey. Thirty-seven surveys were started but not completed. Because personal reminders to complete the survey did not result in a finalization of the survey, these had to be removed. From one center, we received

TABLE 1 | Comparison of results from Mayorandan et al. and this study.

	Mayorandan et al. [15]	This study
General		
Number of participating centers	21	32
Number of treated patients	168	305
Age range patients	0–24 years	0–41 years
Diagnosis		
Diagnosis through NBS[a]	28/168 patients (17%)/43% of participating centers do not screen	26/32 centers (81%)
Most used biomarker for NBS	Tyr	SA
Mutation analysis performed[a]	58/168 (34.5%)	18/26 centers (69.2%)
NTBC		
Patients treated with NTBC	158/168 (94%)	All (100%)
Mean initial dose	1.7 mg/kg/day	1.0–1.5 mg/kg/day
Mean maintenance dose	1.0 mg/kg/day	0.8–1.0 mg/kg/day
Average daily doses	2	1 or 2
Dietary treatment		
Dietary restriction of Tyr/Phe	All (100%)	All (100%)
Supplementation of Phe	Not mentioned	19/32 centers, depending on Phe concentration (59%)
Metabolic monitoring		
Monitoring of Tyr and Phe	95% of centers	97% of centers
Range of acceptable Tyr concentration	200–800 μmol/L (mean 482)	< 100–600 μmol/L (mean 200–400)
Preferred matrix Tyr + Phe	Plasma (42%) + DBS (48%)	Plasma (64%) + DBS (54%)
Monitoring of SA	Done in 29% of centers	Done in all centers (100%)
Preferred matrix SA	DBS (62%) + urine (81%)	DBS (68%) + urine (57%)
Cut-off SA	Urine<LOD (qualitative)/urine < 0.1 mmol/mol creatine (quantitative)/ plasma: < 0.1 μmol/L	Urine < LOD (qualitative)/ urine < 0.5–2 mmol/mol creatine (quantitative)/DBS: < 0.1 μmol/L/plasma: < 0.01–0.163 μmol/L
Monitoring of NTBC	76% of centers	78% of centers
Preferred matrix NTBC	Serum (76%)	DBS (76%)
Mean target range NTBC+range	30–50 μmol/L (range 20–100)	30–60 μmol/L (range 15–60)
Monitoring of 5-ALA	48% of centers	16% of centers
Monitoring for hepatic malignancy		
Monitoring of AFP	All centers (100%)	All centers (100%)
Liver (and kidney) ultrasound	All centers (100%)	All centers (100%)
Liver MRI	76% of centers	88% of centers
Mean frequency liver imaging	Once a year (All imaging) (62%)	• Every 6 months (Ultrasound) • Once a year (MRI 62.5%)
Ophthalmological examination		
Frequent ophthalmological examination	71% of centers	75% of centers

(Continues)

TABLE 1 | (Continued)

	Mayorandan et al. [15]	This study
Mean frequency of follow-up	Once a year (71%)	Once a year (63%)
Liver transplantation		
Number of patients treated with liver transplantation	29/168 (17%)	54/305 (18%)
Neurocognitive development		
Considered a problem by health professionals?	Not mentioned	Yes (91%)
Detection of poor neurocognitive outcome/learning difficulties[a]	2/28 patients (7%)	9/32 centers (28%)
Monitoring of cognitive performance	Variable (not further elaborated)	Developmental steps/school performance (91%)/IQ measurements (59%)
Pregnancy in TT1		
Experience with pregnancy in TT1	Not mentioned	15.6% of participants
Most important (biochemically) for mother	Not mentioned	Low/undetectable SA concentrations
Most important (biochemically) for fetus	Not mentioned	Phe concentrations within target ranges

Abbreviation: LOD, limit of detection.
[a]No true comparison possible (individual patients assessed by Mayorandan and treatment centers investigated in this study).

two responses, which could be combined. Finally, 32 completed responses were analyzed.

3.1.2 | Center Demographics

The 32 responses from different European metabolic centers came from 16 countries (Figure 1). Of the 32 participants, 28 were pediatricians (87.5%), and four were adult physicians (12.5%).

3.1.3 | Patient Demographics

Together, the 32 responding metabolic centers treated 305 TT1 patients aged from 0 to 41 years. The numbers of out-patient visits per year for different age groups can be found in Figure 2. Answers with respect to follow-up frequency varied most in the age group < 1 year. On average, newborns were seen twice in the first month of life. Children younger than 1 year, between 1 and 12 years old, and between 12 and 18 years old were seen four times per year, and adult patients had, on average, two out-patient visits per year. Most centers reported not having experience with pregnant TT1 patients. However, those who did reported, on average, one out-patient visit per month.

3.1.4 | Diagnosis of TT1

Most centers reported that patients were diagnosed through NBS (26/32, 81.3%), while six centers (6/32, 18.8%) reported that their patients were diagnosed clinically in the absence of NBS (Figure 1). Most of the treating centers with access to regional or national NBS programs for TT1 reported that their NBS program used SA as a biomarker for TT1 (21/26, 80.8%), while five (19.2%) were using Tyr. The most common second diagnostic step in newborns tested positive (usually starting treatment awaiting results) was (repeated) SA measurement, followed by molecular genetic analysis (11/26, 42.3%). Eight centers directly used molecular genetic analysis (8/26, 30.7%), while five centers only repeated SA measurements (some in combination with liver, renal and coagulation tests) (5/26, 19.2%), and two centers performed an enzymatic assay (2/26, 7.8%).

3.1.5 | Treatment of TT1(General)

All centers reported treating their TT1 patients with NTBC in combination with a Phe-and-Tyr restricted diet. Moreover, they all agreed that liver transplantation should be offered if necessary. Natural protein intake consisted mostly of a combination of calculations of total protein and/or Tyr intake, while 11 (11/32, 34%) used an exchange method (1 g of protein = 1 exchange [18]). Eighteen (18/32, 56.3%) centers supplemented Phe in patients with low Phe concentrations, yet the lower level to start supplementing Phe varied widely (20–50 μmol/L). The average dose of Phe supplementation reported was between 15 and 25 mg/kg/day. Seven centers (7/32, 21.9%) reported patients with renal tubular dysfunction who required treatment beyond NTBC. Six centers treated these patients with vitamin D supplementation, either in combination with calcium carbonate (50%) or sodium or potassium citrate (50%), while one center treated with sodium or potassium citrate only.

TABLE 2 | Comparison of papers with recommendations for diagnosis and treatment of TT1.

	Schiff et al. [12]	De Laet et al. [11]	Mayorandan et al. [15]	Chinsky et al. [13]	Das et al. [17]
General					
Number of participants	19 French+Belgian physicians	Ad hoc working group (not further specified)	21 European centers	US+Canadian professional group	11 German-speaking centers (18 experts)
Number of treated patients	75	Not mentioned	168	> 100 (no absolute number given)	Not mentioned
Age range patients	Not mentioned	Not mentioned	0–24 years	Not mentioned	Not mentioned
Recommendations					
Diagnosis					
Diagnosis through NBS	No recommendations	Recommended	Recommended	Recommended	Recommended
Recommended biomarker for NBS	—	SA	SA	SA	SA with cut-off > 99.9%
Mutation analysis	No recommendations	May be needed for counselling and family screening.	Not essential for clinical management, but useful for prenatal diagnosis.	-First repeat diagnostic SA. -*FAH* sequencing as confirmatory test, but without delaying initiation of treatment	-*FAH* sequencing as confirmatory test, but without delaying initiation of treatment. -If no variant found → GSTZ1 tested (WES)
Follow-up					
Frequency of outpatient appointments	< 6 m: monthly 6 m–1 year: every 3 months > 1 year: every 4–6 months -Abnormal AFP: every 3 months	< 1 year: monthly > 1 year intervals can be lengthened based on age, severity of disease and compliance (not further specified)	No recommendations	No recommendations (assumed similar to frequency of blood/urine monitoring —see below)	No recommendations

(Continues)

TABLE 2 | (Continued)

	Schiff et al. [12]	De Laet et al. [11]	Mayorandan et al. [15]	Chinsky et al. [13]	Das et al. [17]
NTBC					
NTBC treatment	Offered to every patient	-Initiated upon diagnosis or suspicion of TT1 -Continued without interruption	Initiated as soon as possible after diagnosis	Initiated as soon as possible after diagnosis	-Initiated as soon as possible after diagnosis -Continued without interruption
Mean initial dose	Optimal dosing yet to be determined	-1 mg/kg/day -2 mg/kg/day for 48 h in case of severe liver failure	-1–2 mg/kg/day -2 mg/kg/day in case of severe liver failure	-1 mg/kg/day -2 mg/kg/day in case of severe liver failure	1–2 mg/kg/day
Mean maintenance dose	Optimal dosing yet to be determined	-1 mg/kg/day -Adjust upon NTBC and SA levels	Adjust upon NTBC and SA levels (minimal dose 0.3 mg/kg/day)	Lowest dose to completely suppress urine/plasma SA and keep NTBC levels between 40 and 60 μmol/L	Adjust upon NTBC and SA levels, with lowest possible dose to control SA levels (below detection limit)
Average daily doses	Optimal dosing yet to be determined	No recommendations	-2 doses -1 dose considered in older children to increase compliance.	-2 doses -1 dose+NTBC monitoring may be considered in children > 1 year for convenience.	-2 doses -Patients > 20 kg can be given 1 dose to increase compliance.
Dietary treatment					
Nutritional workup frequency	< 1 year: every 3 months > 1 year: every 6 months	Frequent (not specified)	No recommendations	No recommendations	-Frequent (not specified) -Nutritional consultations by qualified dieticians

(Continues)

TABLE 2 | (Continued)

	Schiff et al. [12]	De Laet et al. [11]	Mayorandan et al. [15]	Chinsky et al. [13]	Das et al. [17]
Dietary restriction Tyr/Phe	No recommendations	-Low Tyr/Phe diet+amino acid supplementation devoid of Phe/Tyr -Continued indefinitely	-Low Tyr/Phe diet+amino acid supplementation devoid of Phe/Tyr -Tyr/Phe calculation justified up to 2 years of age, not necessary in older patients	-Low Tyr/Phe diet+amino acid supplementation devoid of Phe/Tyr -Initiated as soon as possible after diagnosis	-Low Tyr/Phe diet+amino acid supplementation devoid of Phe/Tyr in all patients treated with NTBC
Supplementation of Phe	No recommendations	No recommendations	No recommendations	If Phe < 20 μmol/L consider extra protein intake or Phe supplementation	If Phe < 30 μmol/L consider extra protein intake or Phe supplementation
Metabolic monitoring					
Frequency of Tyr and Phe measurements	< 6 m: Monthly 6 m-1 year: every 3 months > 1 year: every 4–6 months Abnormal AFP: every 3 months	Each visit (see clinical follow-up)	No recommendations	< 1 year: monthly 1–5 years: every 3 months > 5 years: every 6 months	All metabolic monitoring: < 1 year: Every 3 months Childhood: Every 6 months Adulthood: Every 6–12 months
Target range Tyr	400–500 μmol/L	200–400 μmol/L < 12 years, somewhat higher thereafter (not specified)	< 400 μmol/L	200–600 μmol/L	200–600 μmol/L
Target range Phe	No recommendations	No recommendations	No recommendations	20–80 μmol/L	In lower reference range (not specified)
Preferred matrix Tyr + Phe	Plasma	Plasma	DBS + plasma	Plasma	DBS

(Continues)

TABLE 2 | (Continued)

	Schiff et al. [12]	De Laet et al. [11]	Mayorandan et al. [15]	Chinsky et al. [13]	Das et al. [17]
Frequency of SA measurements	See frequency of Tyr/Phe measurements	Each visit (see follow-up)	No recommendations	< 1 year: monthly 1–5 years: every 3 months > 5 years: every 6 months	See frequency of Tyr/Phe measurements
Preferred matrix SA	No recommendations	Plasma, DBS or urine	Urine/DBS	Plasma/DBS. Urine only if blood is not available	DBS/urine
Cut-off SA	No recommendations	No recommendations	Below detection limit	No recommendations	Below detection limit
Frequency of NTBC measurements	< 6 m: monthly 6 m-1 year: every 3 months > 1 year: every 6 months	Each visit (see clinical follow-up)	No recommendations	< 1 year: monthly 1–5 years: every 3 months > 5 years: every 6 months	See frequency of Tyr/Phe measurements
Preferred matrix NTBC	Plasma	Plasma	Serum	Plasma or DBS physicians choice	Plasma/DBS
Target range NTBC	No recommendations	30–50 μmol/L	20–40 μmol/L	40–60 μmol/L	20–60 μmol/L
Home sampling (DBS)	No recommendations	DBS convenient for home sampling	DBS convenient for home sampling	No recommendations	DBS convenient for home sampling and should be offered in between patient visits.
Hepatic follow-up					
Frequency of hepatic workup	< 6 m: monthly 6 m-1 year: every 3 months > 1 year: every 4–6 months Abnormal AFP: every 3 months	Each visit (see follow-up)	No recommendations	< 1 year: monthly > 1 year: yearly	< 1 year: every 3 months Childhood: every 6 months Adulthood: every 6–12 months

(Continues)

TABLE 2 | (Continued)

	Schiff et al. [12]	De Laet et al. [11]	Mayorandan et al. [15]	Chinsky et al. [13]	Das et al. [17]
Frequency of AFP measurements	Same frequency as hepatic workup	-Each visit (see clinical follow-up). -Target cut-off close to normal: 10 ng/L -Slow decrease → referral to liver transplant team	Every 3–6 months	Every 6 months	Every 6–12 months
Liver ultrasound	Every 6 months	Every 6 months	Every 6 months	Yearly	-Every 6–12 months -Immediate imaging in the absence of normalisation or secondary rise in AFP
Liver imaging (CT/MRI)	< 1 year: every 6 months > 1 year: yearly Abnormal AFP: every 6 months	-Yearly. (consider once every 2 years in patients detected by NBS) -Preferred if nodules are seen on US. Frequency not specified	Yearly. MRI recommended when malignancy is suspected	Yearly (US OR CT OR MRI)	If HCC is suspected
Liver transplantation	Performed in HCC, liver failure or NTBC resistance	Indications: acute liver failure and malignancy	Therapy of choice in HCC	-Limited to malignancy, decompensated liver disease or NTBC failure (or unavailability)	-Performed in HCC, therapy-refractory liver failure or chronic liver failure despite NTBC treatment.
			Other indications: NTBC resistance and liver failure	-SA remains slightly elevated after transplantation, therefore, periodic screening for renal disease warranted.	-No treatment needed after transplantation

(Continues)

TABLE 2 | (Continued)

	Schiff et al. [12]	De Laet et al. [11]	Mayorandan et al. [15]	Chinsky et al. [13]	Das et al. [17]
Renal monitoring					
Renal workup (including renal blood work [e.g., bicarbonate, creatinine], and urine renal analyses)	< 6 m: every months 6 m-1 year: every 3 months > 1 year: every 6 months	Every visit (see clinical follow-up)	No recommendations	Yearly	Included in regular monitoring: < 1 year: every 3 months Childhood: every 6 months Adulthood: every 6–12 months
Ophthalmological monitoring					
Frequency of follow-up (slit lamp)	Yearly	Periodic slit lamp examination may be indicated (not further specified)	Yearly	When symptomatic or at increased risk. (no clear consensus on yearly evaluation)	Routine ophthalmological follow-up is not recommended. Only done upon symptoms or poor dietary control.
Neurocognitive development					
Considered a problem by health professionals?	Yes	Yes	Not mentioned	Yes	Yes
Monitoring of cognitive performance	-At start of NTBC treatment -12 M after start NTBC treatment -Yearly or according to local settings thereafter	-Little predictive value < 4 years -First assessment before school entry -Thereafter intervals according to apparent progress	Regular psychomotor assessment (not specified)	Before school age or as needed	When entering school and at regular intervals thereafter (not specified).
Bone density					
Osteodensitometry	According to local settings/ twice a year	-Should be check for any patient on diet -Important for patients with persisting renal tubular disease -No recommendations on frequency	No recommendations	Risk of osteopeniasimilar to other individuals on restricteddiet. If RTA present, monitoring is required	No recommendations

(Continues)

TABLE 2 | (Continued)

	Schiff et al. [12]	De Laet et al. [11]	Mayorandan et al. [15]	Chinsky et al. [13]	Das et al. [17]
Pregnancy in TT1					
Experience with pregnancy in TT1	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Clinical experience limited
NTBC use during pregnancy	No recommendations	IF NTBC is proven to be completely safe, it might be given to the mother to prevent damage in utero. This approach should be regarded as experimental and subject to a research protocol	No recommendations	-No clear consensus on the use of NTBC during pregnancy -Follow-up should be performed on infants born to women treated with NTBC during pregnancy	-NTBC shall be continued during pregnancy. -Metabolic control should be stable preconceptionally
Breastfeeding	No recommendations	No recommendations	No recommendations	Contraindicated while treated with NTBC	Not encouraged based on lack of evidence.

3.1.6 | Treatment With NTBC

3.1.6.1 | Dosing. Doses of NTBC used in patients diagnosed either by NBS or clinically are depicted in Figure 3A. Most centers (17/26, 65.4%) used the same *initial* dose of NTBC in patients diagnosed by NBS and those diagnosed clinically. Nine centers (9/26, 34.6%) used higher *initial* doses of NTBC (0.5–1.0 mg/kg/day higher) in patients who were clinically diagnosed compared to patients who were diagnosed by NBS. All centers responded using on average the same *maintenance* dose in patients diagnosed by NBS and those diagnosed clinically.

Across centers, initial NTBC doses of 1.0–1.5 mg/kg/day were most often used (both after NBS and for clinically diagnosed patients). The most used maintenance doses of NTBC were between 0.8 and 1.0 mg/kg/day. Regarding NTBC administration, 17 centers used two daily doses of NTBC in all patients (17/32, 53.1%), five used one daily dose in all patients (5/26, 15.6%), four used two daily doses in childhood and one in adulthood (4/32, 12.5%), and six used two daily doses in early childhood and one at increasing age, depending on the patient's preference and compliance (6/26, 23.01%). Centers relied on a combination of SA and NTBC measurements at follow-up for NTBC dosing rather than PSA, 5-ALA, AFP, or liver imaging (Figure 3B).

3.1.7 | Adverse Events/Observations

Centers were asked about the *clinical* and *biochemical* signs of suboptimal NTBC treatment and side effects of NTBC in their patients (Figure 4). Neurological symptoms and acute porphyric attacks were considered the most indicative *clinical* sign of suboptimal NTBC treatment, and (high) SA concentrations were the most indicative *biochemical* sign. Many centers did not encounter any side effects from NTBC in their patients. However, if side effects were seen, the most common were ophthalmologic problems. To keep track of these ophthalmologic problems, most centers advised ophthalmologic follow-up for their patients once a year (20/32, 62.5%). Four centers (4/32, 12.5%) advised ophthalmologic follow-up once every 2 years, and eight (8/32, 25%) advised ophthalmic follow-up only in case of symptoms.

3.1.8 | Metabolic Monitoring in TT1

Results show that TT1 was mainly monitored using a combination of frequent measurements of SA, NTBC, Tyr, Phe, and AFP concentrations (Figure 5A). Preferred matrices for measuring the different metabolites are shown in Figure 5B. Lower and upper therapeutic ranges for biochemical parameters varied widely between the centers (Figure 5C). However, the most frequent target ranges for NTBC, Tyr, and Phe were 30–60 μmol/L, 200–400 μmol/L, and 30–80 μmol/L, respectively.

Five centers also reported measuring 5-ALA for follow-up of TT1, and nine reported the preferred matrix for 5-ALA measurements, despite four reported not measuring it frequently (Figure 5B).

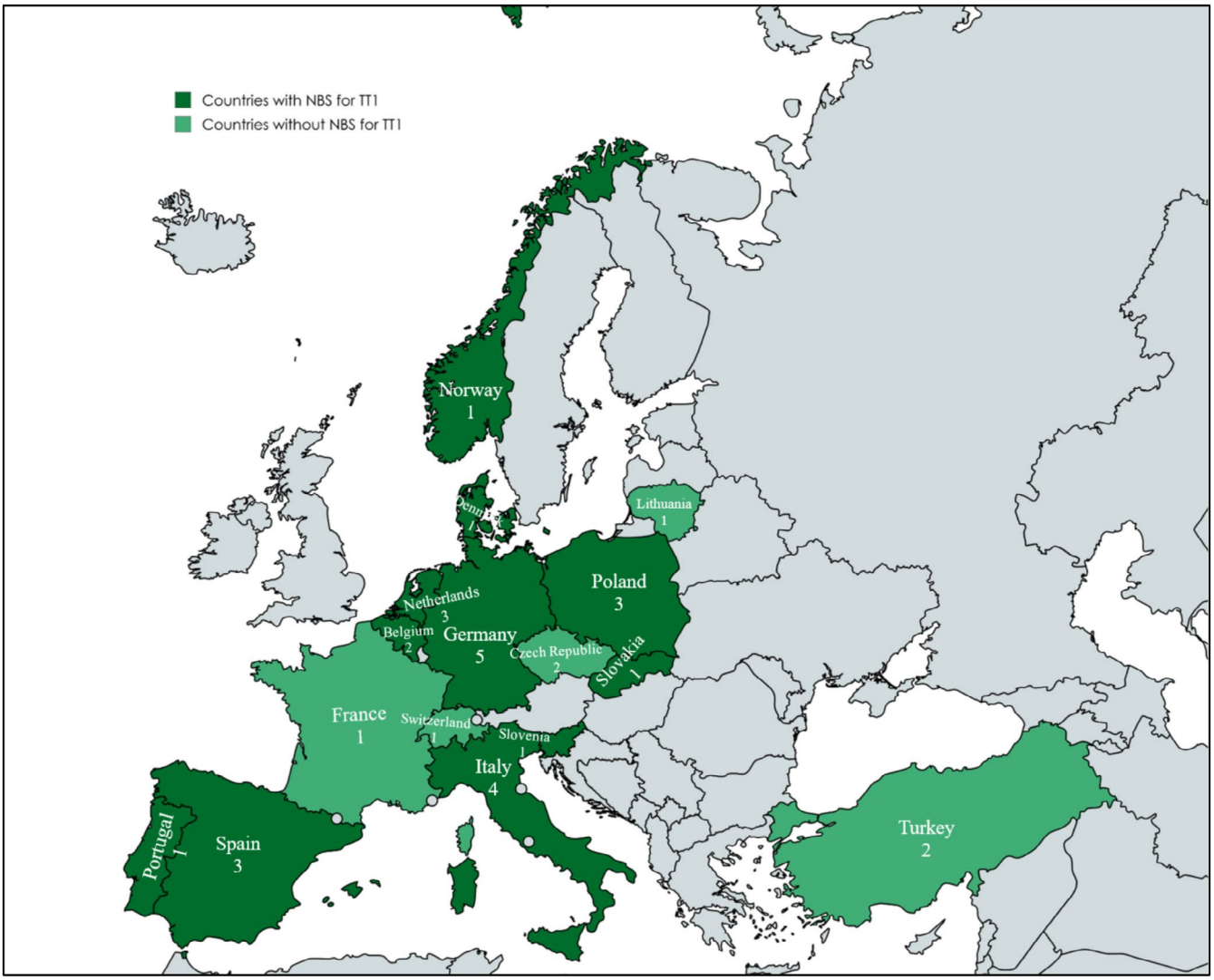

FIGURE 1 | Responses per country; Dark green indicate countries with newborn screening for Tyrosinemia type I and light green indicate countries without newborn screening for tyrosinemia Type I.

The five centers that measure 5-ALA reported doing so with a frequency of once every 6 months. Only one center reported measuring porphobilinogen synthase activity (PSA) regularly, once every 6 months or until normalization. Three centers reported frequently measuring PSA, with a preferred matrix being either dried blood spot (DBS), serum, or plasma (Figure 5B).

Thirteen out of 32 centers skipped the question to report the laboratory thresholds for DBS SA (μmol/L), urine SA (mmol/mol creat) and plasma SA (μmol/L) concentrations. Twenty (20/32, 62.5%) centers used DBS SA, of which 18 reported their laboratory cut-off values, and these ranged from 0.1 to 7.32 μmol/L, with 0.1 μmol/L being the most frequently reported cut-off value. Four centers exclusively used urine SA (3 by qualitative and 1 by quantitative GC–MS measurements, cut-off range < 0.5–2 mmol/mol creat), 13 used both qualitative urine SA measurements and quantitative DBS measurements, and two measured plasma SA, using cut-off values of 0.01 and 0.163 μmol/L, respectively.

Ten centers corrected for the differences in plasma and DBS concentrations (11/32, 34.4%), using a laboratory-specific correction factor, yet most of them corrected for this difference only for Phe concentrations. DBS Phe concentrations were converted to plasma values with correction factors ranging from 1.2 to 1.4.

3.1.9 | Frequency of Monitoring

As with the therapeutic ranges, frequency of sampling also varied largely between the centers. Frequency of sampling at the age 0–4 years was taken as reference. Centers could then indicate if and how the frequency of monitoring in their center differed with the patient's age.

The most reported frequency of sampling at age 0–4 years for all regularly monitored biochemical markers in TT1 (NTBC/SA/Tyr/Phe and AFP) was *once every 3 months* (Figure 6A). Frequency of monitoring did not change with increasing age in 11 centers (11/32, 34.4%), while 17 centers (20/32, 62.5%) decreased the frequency of metabolic monitoring with increasing age. For patients from 4 years onward, the most reported frequency of monitoring NTBC/SA/Tyr/Phe and AFP was once every 6 months (Figure 6B). One center determined frequency of monitoring solely on the basis of metabolic balance.

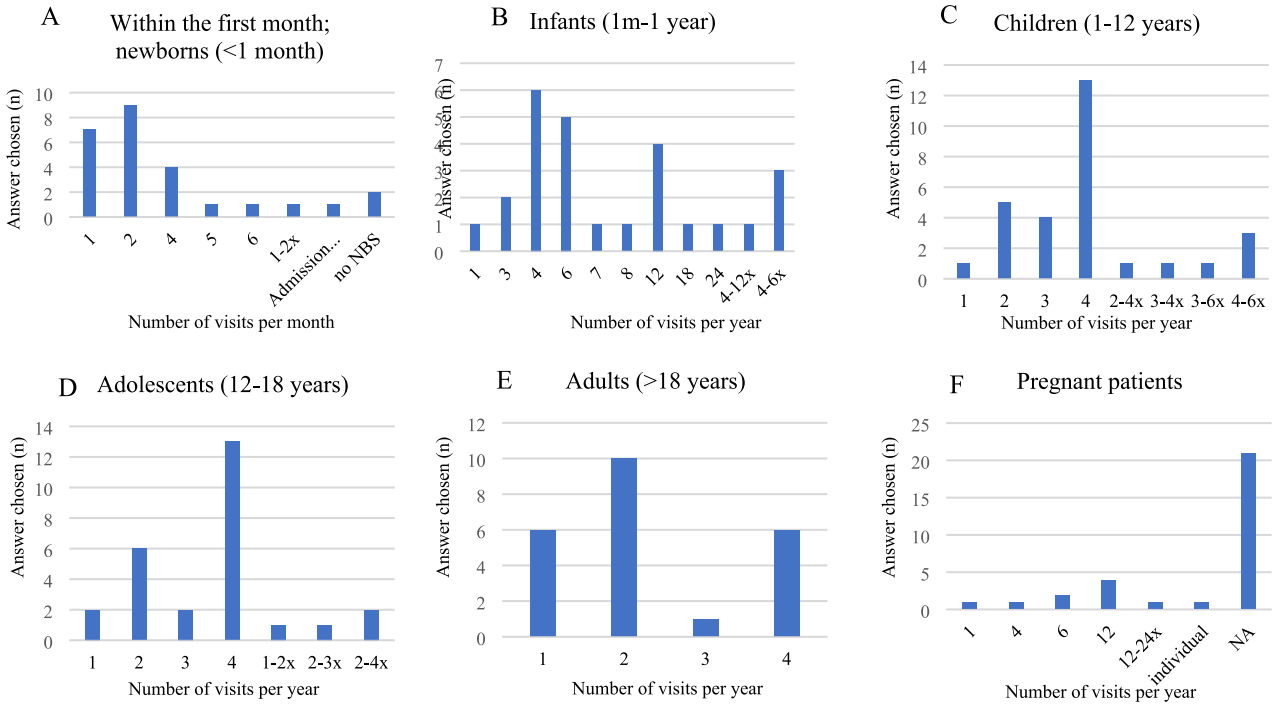

FIGURE 2 | Number of out-patient visits: Y-axes: Absolute number of times an answer was given, X-axes: Frequency of out-patient visits in absolute numbers. (A) Number of visits during the first month of life, (B–F) number of visits per year for different age groups from 1 month to adulthood, and during pregnancy. Number of responses can differ (e.g., 25 in A and 28 in D) depending on which kind of patients physicians treat, for example child physician, adult physician or both.

Four centers (4/32, 12.5%) decreased the frequency of metabolic monitoring after the ages of 12 (2) or 18 (2) years. In three centers, the frequency of AFP, Tyr, and Phe measurements decreased from once every 3 months to once every 6 months, and in one center, the frequency of NTBC, SA, Tyr, and Phe measurements changed from twice per month to once per month after 12 years of age. The frequency of measuring the other parameters remained the same as the frequencies reported in the group of patients > 4 years old. Most centers (14/32, 43.8%) reported always taking samples for metabolic measurements at the same time, relative to food intake. Six centers (6/32, 18.8%) obtained overnight fasted samples, four (6/32, 18.8%) solely around the same time during the day, and another six (6/32, 18.8%) did not take samples at specific times.

3.1.10 | Monitoring for Hepatic Malignancy

All centers reported screening for hepatic malignancy by frequent AFP measurements and ultrasound. In addition, 20 centers (20/32, 62.5%) also performed regular MRIs to rule out malignancy, usually once per year. Eight centers (8/32, 25%) used MRI only in case of abnormalities on ultrasound or steep AFP rise, and four (4/32, 12.5%) did not use MRI at all. The majority of centers (18/32, 56.3%) did not decrease the frequency of monitoring for hepatic malignancy with increasing age. Some reported that frequent monitoring is required for reimbursement of NTBC treatment. Six (6/32, 18.8%) reduced the frequency of monitoring in patients diagnosed by NBS compared to clinically diagnosed patients, another six (6/32, 18.8%) reduced the frequency of monitoring in case of stable AFP concentrations, yet target AFP values differed (range between ≤ 3 μg/L to < 12 μg/L). Two centers (2/32, 6.3%) reported decreasing the frequency of monitoring once patients reach adulthood (> 18 years old).

3.1.11 | Neurocognition in TT1

The vast majority of centers considered neurocognitive problems to be an issue in TT1 patients (29/32, 90.6%), yet three centers considered it not to be of much clinical interest (3/29, 9.4%). Nine (9/32, 28.1%) centers encountered patients with problems in neurocognitive development. Monitoring of neurocognition was mostly achieved through a combination of evaluating developmental steps and school performance (29/31, 90.6%) and testing IQ (19/32, 59.4%). Moreover, 10 centers (10/32, 31.3%) occasionally performed formal neuropsychological examinations, while four (4/32, 12.5%) only investigated neurocognitive performance on a research basis.

3.1.12 | Pregnancy in TT1

Only five centers reported having experience with pregnancy in TT1 patients (15.6%). All centers (including those who did not have experience with pregnancy in TT1) were asked what they considered to be the most important (biochemically parameter) in the case of pregnancy during NTBC treatment, both for the mother and for the fetus. Six centers did not fill in this question (6/32, 18.8%). The remaining responders answered that they considered it most important to maintain SA concentrations low/undetectable for maternal health, while Phe concentrations within target ranges were considered most important for fetal health.

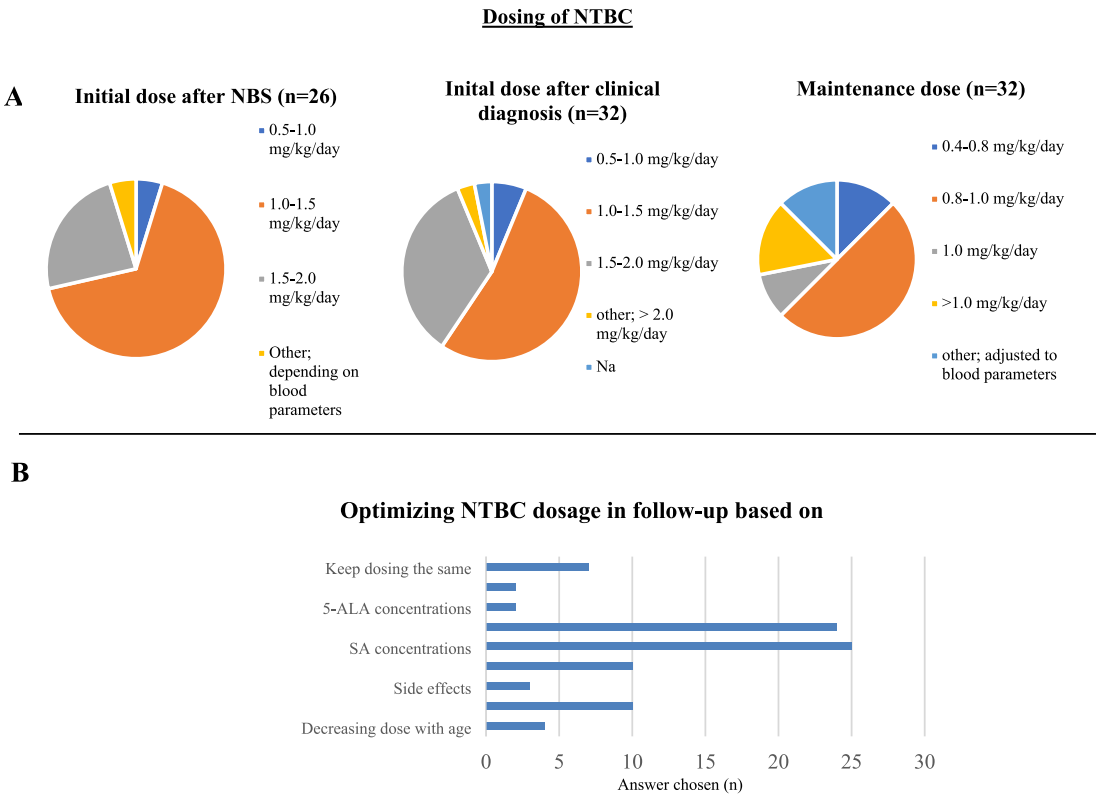

FIGURE 3 | Dosing of NTBC. (A) NTBC dose after initial diagnosis (both clinical and through NBS), and maintenance dose. Pie-charts divide absolute number of responses. (B) Methods for optimization of NTBC dosage. 5-ALA, 5-aminolevulinic acid; AFP, alpha fetoprotein; NA, not applicable; PSA, porphobilinogen synthase activity; X-axis, number of times an answer was chosen in absolute numbers; Y-axis, item possibly important for optimizing NTBC dosing.

3.1.13 | Liver Transplantation in TT1

Of all centers, 18 (18/32, 56.3%) treated patients received a liver transplantation. The total number of transplanted patients among all participants was 54 (54/305, 17.7%). The youngest patient receiving a liver transplant was 3 months old, while the oldest was 33 years old. Centers agreed that it is most important to offer liver transplantation to 1. Any TT1 patient with a hepatic nodule suggestive of HCC, irrespectively of a rise in AFP (27/32, 84.4%), 2. any patient with liver failure who is not responding to NTBC treatment (21/32, 65.6%), and 3. any patient with a hepatic nodule and a rise in AFP (17/32, 53%).

3.2 | Aim 2: Comparison Between Results of Mayorandan et al. and This Study

We compared our results with data of Mayorandan et al. [15]. Results can be found in Table 1. More patients are nowadays identified by NBS (81% compared to 17%). Current NTBC doses tend to be lower than in 2014. Furthermore, low Phe concentrations and supplementation, neurocognitive development, and pregnancy are now upcoming issues that were not discussed in 2014.

3.3 | Aim 3: Alignment of Results With Previously Published Recommendations

Five recommendations papers for diagnosis and treatment of TT1 have been published between 2012 and 2025 [11–13, 15, 17]. Two studies evaluated management-based recommendations on their survey data (Schiff et al. and Mayorandan et al.) [12, 15], one study based recommendations on existing literature (de Laet et al.) [11] and two studies based the recommendations on consensus group meetings with experts in the field (Chinsky et al. and Das et al.) [13, 17] Below, all published guidelines are compared (Table 2). In general, many recommendations remained unchanged over the years. Nonetheless, in the more recent recommendations (after 2017), there is growing attention in treating hypophenylalaninemia with Phe supplementation. Moreover, the recommended frequency of liver disease monitoring decreased over time (from once every 3 months in the earlier studies to once a year recently). Regarding pregnancy, earlier guidelines did not have any recommendations due to lack of cases and data published. Currently, more interest is shown in the management of pregnancy and breastfeeding in TT1. While data remain scarce, there are now some recommendations concerning pregnancy and breastfeeding in TT1, namely to continue NTBC during pregnancy, but to discourage breastfeeding while on NTBC.

4 | Discussion

Since the introduction of NTBC 32 years ago, management and outcome of TT1 has significantly improved [1, 3, 19]. Combined with the shift to early diagnosis by NBS, TT1 patients can now be treated with NTBC pre-emptively, which largely, if not completely, prevents classic symptomatology [4]. Therefore, TT1 patients are now able to age, which was previously considered

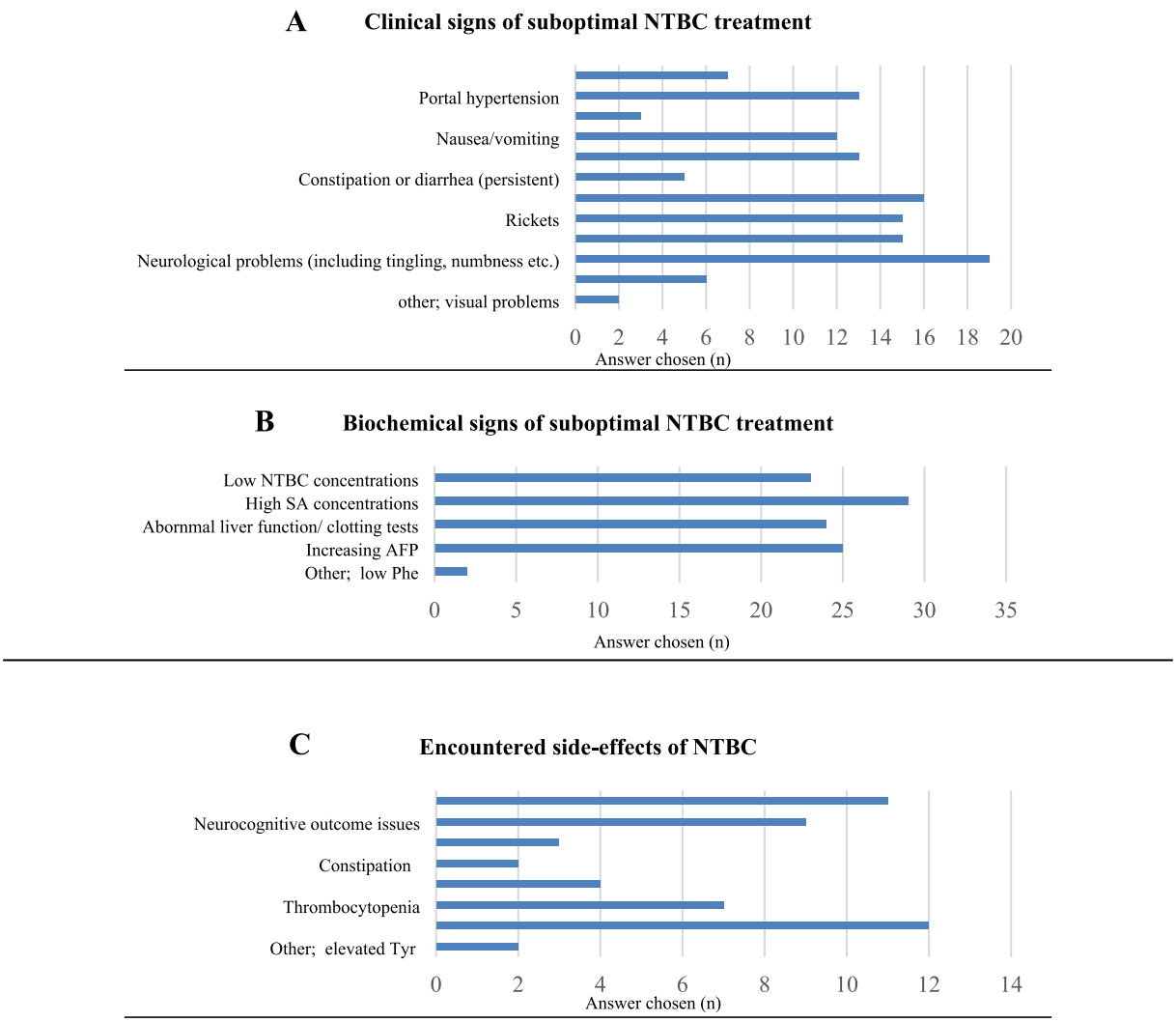

FIGURE 4 | Suboptimal dosing and adverse effects of NTBC. (A) Clinical signs of suboptimal NTBC dosage according to responders. (B) Biochemical signs of suboptimal NTBC treatment according to responders. (C) Adverse effects of NTBC encountered by responders. X-axes: Absolute number of times an answer was given for each specific item on the y-axis. Multiple answers from one participant were allowed.

impossible without liver transplantation, and treatment goals shifted from crisis treatment to long-term care. To evaluate the risk of developing complications upon aging, due to TT1 or its treatment, long-term follow-up remains essential.

In this study, we evaluated the current European practice of 32 centers accounting for the treatment of 305 TT1 patients and compared data to those shown by Mayorandan et al. in 168 patients in 2014 [15]. Our survey showed that management of TT1 still differs widely across European metabolic health care centers despite there also being many similarities. Most notably, more patients are now identified by NBS, NTBC dosage is lower than in 2014, and there has been a shift in focus from hepatic disease only to hepatic-neurological symptoms during long-term treatment.

Comparison of previous TT1 recommendations over the last 12 years also showed a growing emphasis on minimizing NTBC dosage, addressing hypophenylalaninemia, reducing the frequency of hepatic malignancy screening, and increasing the attention to pregnancy management, breastfeeding, and neurocognitive outcome, which was also reflected in our results.

Before discussing the results further, some limitations should be mentioned. Despite our efforts, not all contacted centers responded to the survey, and attempts to obtain completed responses from partially completed surveys were not always successful. This may have introduced non-response bias, potentially affecting the validity of the study and limiting the generalizability of the findings.

When looking at the results, most TT1 patients are now diagnosed by NBS via elevated DBS SA concentrations, which is a large improvement compared to 2014, when only 17% of patients were identified by NBS [15]. SA is preferred over Tyr as a screening marker due to its higher positive and negative predictive values for TT1 [20, 21]. Nonetheless, similar to clinical practice, NBS for TT1 differs worldwide, especially in terms of analytical methods and cut-off values [20, 22], and some centers reported high false-positive results and low Positive Predictive Value (PPV) when using SA [22]. Van Vliet et al. showed that

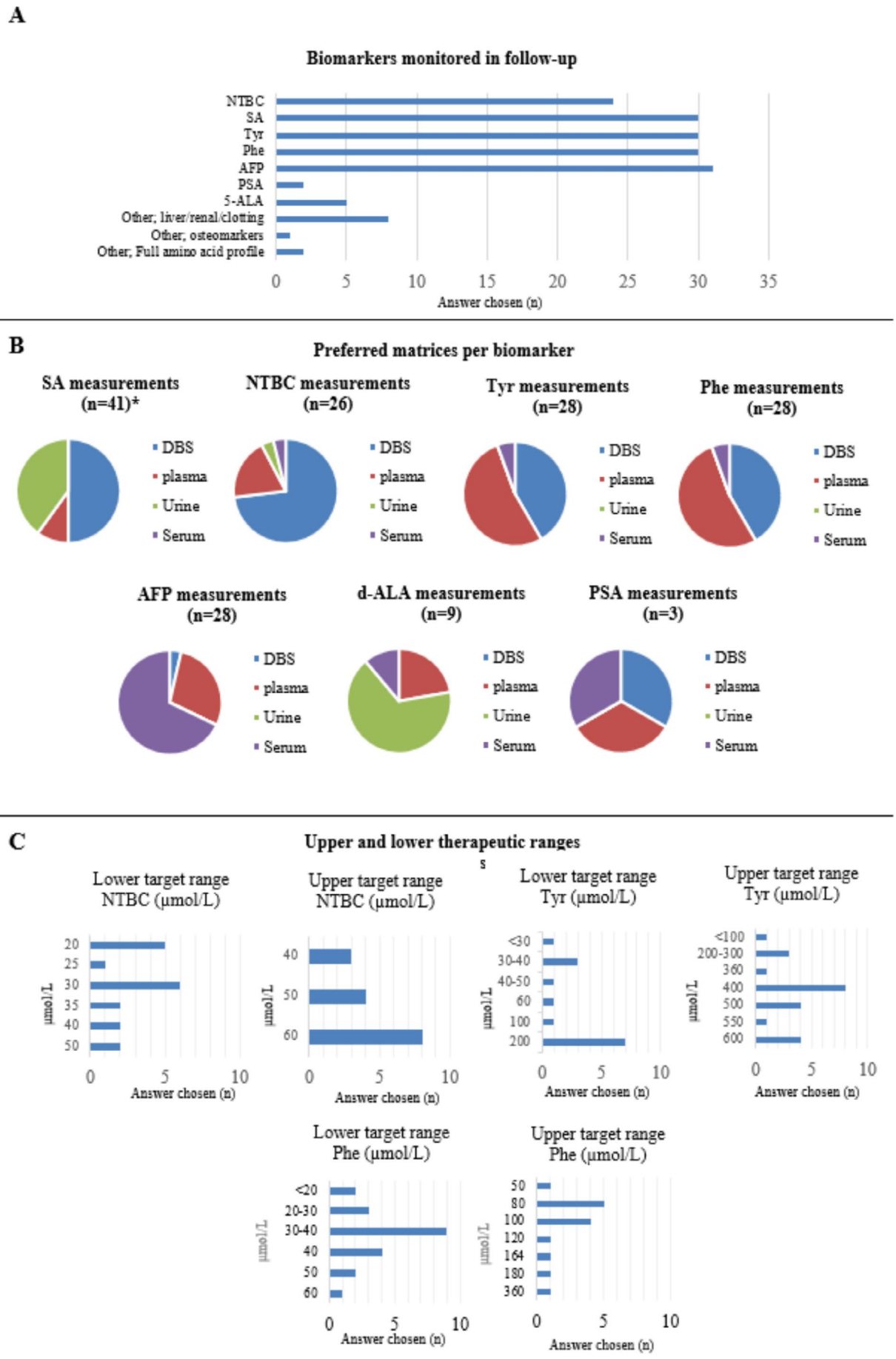

FIGURE 5 | Legend on next page.

FIGURE 5 | Metabolic monitoring in TT1. (A) Overview of biochemical markers frequently monitored in TT1patients according to responders. (B) Preferred matrices for the monitored markers according to responders. Pie charts divide absolute number of responses. (C) Target values for different markers. X-axes (A+C): Absolute number of times an answer was chosen. 5-ALA, 5-aminolevulinic acid; AFP, alpha fetoprotein; PSA, porphobilinogen synthase activity. * indicates multiple answers per participant allowed.

this may be because children with maleylacetoacetate isomerase deficiency (MAAI-D), which appears to be clinically insignificant [23, 24] and can easily be differentiated from TT1 by measurement of elevated maleic acid in urine [25], are also detected in SA-based screening. It needs to be proven whether maleic acid measurements in DBS as a second-tier method could improve the PPV of NBS for TT1. Recent work from Bouva et al. showed that adding existing biomarkers alongside SA as secondary screening markers already significantly improves the PPV of the NBS for TT1 [26].

With regard to treatment, current NTBC dosages are lower than 10 years ago (0.8–1.0 mg/kg/day vs. 1–1.5 mg/kg/day) [15]. Some centers still use higher initial doses (1.5–2.0 mg/kg/day) in clinically diagnosed patients with liver failure, as previously recommended by de Laet et al. [11] Many centers reduced maintenance doses based on SA and NTBC concentrations, in line with recent recommendations to use the lowest effective dose to maintain adequate NTBC and SA concentrations [17]. NTBC monitoring permits this dose adjustment to the lowest effective level required to suppress SA [13]. One case report showed that ≥ 0.55 mg/kg/day NTBC improved clinical outcome (during follow-up of 27 months and 10-year follow up) [27], while doses < 0.55 mg/kg/day resulted in detectable SA concentrations without other abnormalities [28].

Most centers advised twice-daily NTBC dosing (at least in childhood), with many switching to one-daily in adults per request or to reduce non-compliance. While literature is inconclusive, twice-daily dosing may prevent side effects from NTBC, ensure more stable suppression of toxic metabolites, and may decrease the necessary total dose [29–32]. NTBC's long half-life (54 h) may support once-daily dosing in healthy adults [30], but individual pharmacokinetics may vary and are not well documented [31, 32]. Moreover, impaired liver function may prolong the half-life of NTBC and increase toxicity risk [30]. Twice-daily dosing leads to significantly lower median doses in patients, suggesting that this regimen may be particularly beneficial for those with impaired liver function [29].

With regard to follow-up, metabolites were regularly monitored. SA (measured to evaluate the effects of TT1 itself and to monitor treatment (combined with NTBC levels)), Tyr and Phe levels (measured to assess side-effects of NTBC) were most regularly measured. The frequency of these measurements in our study followed existing recommendations: monthly during the first year of life, every 3 months until age five, and every 6 months thereafter [13]. NTBC levels (to assess treatment efficacy) were measured less frequently. The reason for this may be that elevated SA was considered the main indicator of suboptimal NTBC treatment, and analysis of NTBC is less widely available. NTBC measurements lack standardization, which may also have contributed to the reported lower measuring frequency [33–37]. Moreover, NTBC measurements are affected by inter-individual differences in drug metabolism and variability in target ranges (typically 30–60 μmol/L in DBS, ranges 15 to 60 μmol/L), especially since concentrations differ when measured in different matrices [8].

Dependent on derivatisation method and instrumentation, analytical challenges also apply to measurements of SA due to low ion intensities (due to contamination of the mass spectrometer, low instrument sensitivity or poor ionization efficiency), which complicates accuracy and precision in the lower ranges and cut-off determination [38]. This could have caused the widely varying SA target ranges (< 0.1 to < 7.32 μmol/L). SA measurement in DBS is especially challenging. As a result, qualitative urine tests are still commonly used. However, advances in equipment sensitivity over the years [39, 40] have enabled more centers to quantify SA in DBS or plasma—with a resulting increase in SA monitoring in our study compared to the 2014 findings [15].

For Tyr, most centers followed recommended target values of 200–400 μmol/L, being in line with de Laet et al. [11] and Mayorandan et al. [15] or 200–600 μmol/L, in line with Das et al. [17], yet upper targets ranged from < 100 to 600 μmol/L. High Tyr levels (> 800 μmol/L) have been associated with ocular problems in some studies [15, 41], yet not all studies confirm such findings [42]. It is also suggested that high Tyr levels may contribute to the suboptimal neurocognitive development in TT1 patients [43]. Interestingly, the study of Barone et al. showed that even physiological Tyr concentrations can decrease the activity of cerebral tryptophan hydroxylase activity [44]. In daily practice, Tyr concentrations above 400 μmol/L are commonly seen in patients with poor dietary compliance, and are also a known side effect of NTBC treatment. Adherence to Tyr targets may be difficult, and more research is needed on the possible relationship between Tyr concentrations and outcome, both neurocognitive and ophthalmological.

Acceptable limits of Phe concentrations also varied (range < 20 to 60 μmol/L). This reflects the ongoing debate regarding the clinical significance of low Phe concentrations in TT1 [45]. About half of centers considered Phe supplementations necessary in hypophenylalaninaemia. As described in PKU [46, 47], low Phe concentrations may play a role in the pathophysiology of neurocognitive deficits and poor growth in TT1 patients [48, 49].

Screening for malignancy remains important in TT1 management in 2025, especially if NTBC is started after 2 months of age [19], acknowledging that regeneration already starts prenatally [50]. For now, patients diagnosed by NBS are not considered at an increased risk for HCC if treatment is well maintained, which could explain why recent guidelines state less frequent liver screening than previous recommendations [13, 19] For example, AFP (strongly related to HCC [12, 19]) assessment is now every 6 months (vs every 3 months) and liver ultrasound every 6 months (vs every 3–6 months previously) [13, 14, 16].

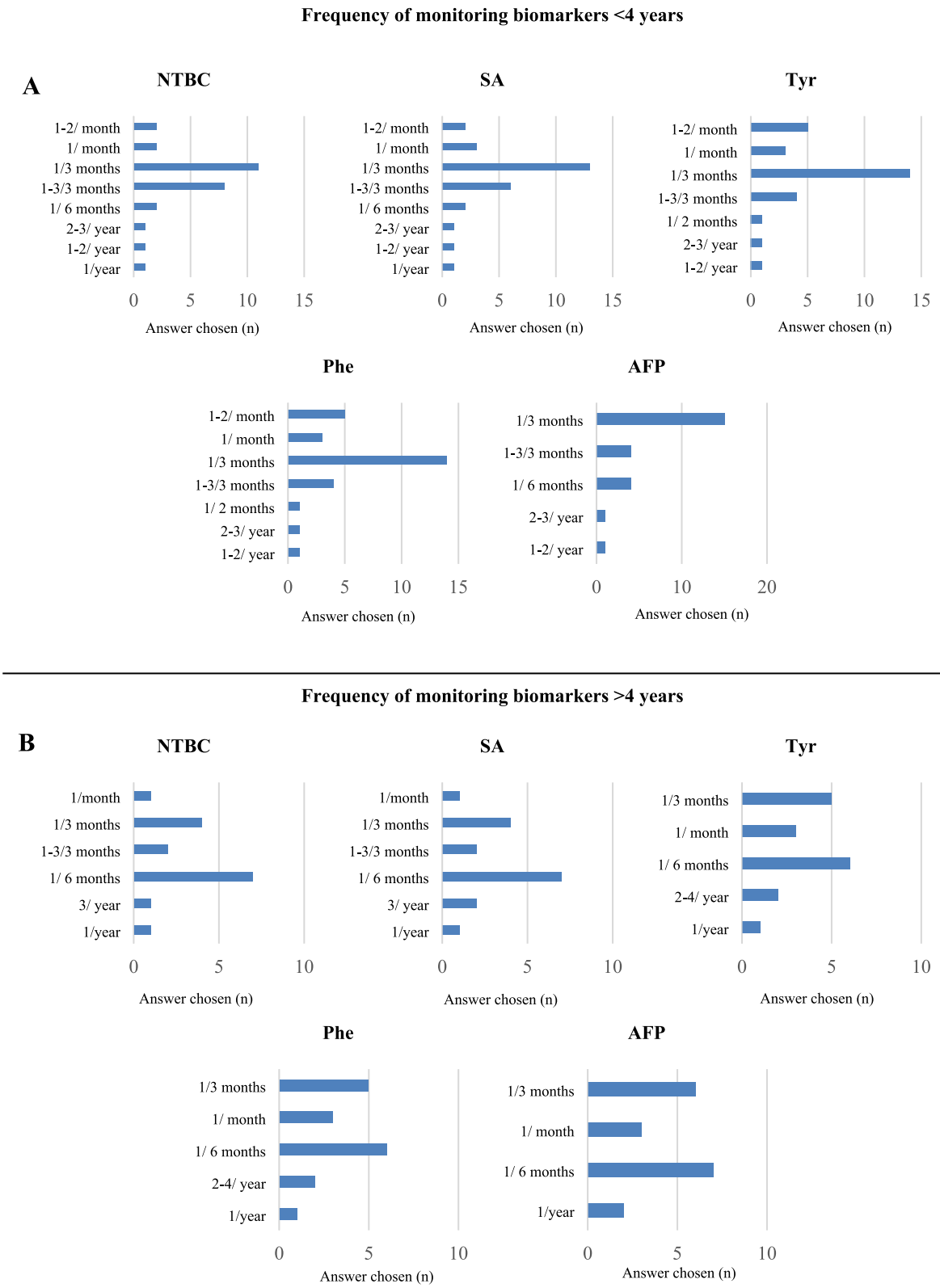

FIGURE 6 | Frequency of metabolic monitoring in TT1 in different age groups. Y-axes: frequency of monitoring, X-axes: Absolute number of times an answer was chosen. (A) Frequency of monitoring in patients < 4 years old. (B) In case of different frequencies depending on age, frequency of monitoring > 4 years old. X-axes: number of times answer was chosen. * Example: 1–3/3 months meaning 1–3 times per 3 months.

Ultrasound has proven to be effective in detecting liver masses suspicious for malignancy, at least also depending on the operator's experience and the quality of the technical equipment [51]. Some studies suggest that MRI is superior in detecting liver masses [17, 52]. However, compared to ultrasound, MRI is expensive and requires anaesthesia/sedation in younger patients. This may explain why many only perform an MRI in case of abnormalities on ultrasound or do not use MRI at all.

Nonadherence to treatment was reported by some centers, though only two previous studies quantified this (in 15% of patients) [53, 54]. This issue needs to be addressed when drafting future guidelines, as the long-term impact of poor NTBC adherence on liver and kidney health is unclear but potentially serious. Nonadherence can also result in acute porphyric attacks [7], a medical emergency requiring fast reinitiation of NTBC and treatment with Haemarginate, the treatment of choice in acute porphyric attacks due to primary delta-aminolevulinic acid dehydratase deficiency [55]. In mice, long-term noncompliance with NTBC treatment is the main cause of HCC development in TT1 later in life [56]. More frequent measurements of SA, NTBC, and Tyr [55] might help detect and improve poor treatment adherence early on [35, 37, 40, 57]. DBS home sampling can increase the frequency of blood measurements without increasing the number of outpatient visits and should be offered to patients. Unfortunately, AFP measurements are not yet regularly offered in DBS (despite a 2019 study proving its feasibility) [58], but this could further contribute to a decrease disease burden in patients.

Two emerging topics not discussed by Mayorandan et al. have gained growing attention in recent years. First, nearly all centers considered neurocognitive issues as concerning in TT1. Suboptimal neurocognitive outcome has been suggested to be a side effect of NTBC treatment that can partly be explained by high Tyr concentrations [48]. Clear, uniform, target ranges for Tyr and Phe seem crucial to minimize neurocognitive deficits in TT1 [43]. However, despite growing concern, there is no standardized method or recommended frequency for assessing neurocognitive outcomes in TT1. Studies comparing neurocognitive outcome in TT1 and PKU patients show that TT1 patients may be more severely affected in similar cognitive domains [48]. Recently revised European PKU guidelines (2025) recommend neuropsychological assessments—including IQ, executive function, and attention—at ages 5, 12, 18, and every 5–10 years thereafter [59]. Given the metabolic similarities and assumed similarly affected neurocognitive domains [48], these PKU guidelines could serve as a blueprint for developing comparable assessment protocols in TT1. Moreover, to further understand neurocognitive impairment in TT1 and its relationship with elevated Tyr concentrations, it may be worthwhile to examine tyrosinemia type 3 (TT3) more closely, for example by prospective NBS cohort studies. In TT3, neurocognitive impairment is more commonly observed than in TT1. Limited research in three TT3 patients has shown that Phe-and-Tyr restricted diets resulted in normal cognitive development in two patients, while one continued to show delayed psychomotor development despite dietary restriction [60].

Secondly, pregnancy in TT1 is becoming more relevant as patients reach adulthood. To protect maternal health, centers considered keeping SA undetectable key, while they also considered maintaining normal Phe levels important for fetal development. High maternal Phe concentration is known to cause complications in PKU (low birthweight, microcephaly and mental retardation) [61], and low Phe may be associated with impaired fetal growth (intra-uterine growth restriction), although the effects are less well known [62]. So far, the few examples of pregnancies in TT1 show no concerning signs from high Tyr concentrations [63–65]. As reports on pregnancies (and breastfeeding) in TT1 patients remain scarce, sharing clinical experiences is essential to guide evidence-based care for both pregnancies and breastfeeding in TT1 patients.

Lastly, our findings showed similar trends in clinical practice when compared to existing recommendations and the data reported by Mayorandan et al. in 2014. It is worth emphasizing that previously published recommendations lack sufficient high-quality data from randomized controlled trials. Conducting such trials remains challenging in the context of a rare disorder, but should be encouraged to create evidence-based guidelines in the future.

5 | Conclusion

Our results highlight that despite many consistencies in the management of TT1, many aspects still also differ widely across European metabolic health care centers, highlighting the need for consistent, updated, and evidence-based clinical guidelines to ensure uniform care.

Author Contributions

A.M.K., **A.M.D.**, **A.M.**, **M.R.H.F.**, **F.J.V.S.:** conceptualization. **A.M.K.**, **M.R.H.F.**, **F.J.V.S.:** data curation. **A.M.K.**, **M.R.H.F.**, **F.J.V.S.:** formal analysis. **A.M.K.**, **M.R.H.F.**, **F.J.V.S.:** investigation. **A.M.K.**, **A.M.D.**, **A.M.**, **M.R.H.F.**, **F.J.V.S.:** methodology. **A.M.K.:** project administration. **A.M.K.**, **A.M.D.**, **A.M.**, **M.R.H.F.**, **F.J.V.S.:** resources. **A.M.K.**, **A.M.D.**, **A.M.**, **M.R.H.F.**, **F.J.V.S.**, **The TT1 MetabERN Professional Collaboration Group:** data curation. **M.R.H.F.**, **F.J.V.S.:** supervision. **M.R.H.F.**, **F.J.V.S.:** validation. **A.M.K.**, **M.R.H.F.**, **F.J.V.S.:** visualization. **A.M.K.**, **M.R.H.F.**, **F.J.V.S.:** writing – original draft preparation. **A.M.K.**, **A.M.D.**, **A.M.**, **M.R.H.F.**, **F.J.V.S.**, **The TT1 MetabERN Professional Collaboration Group:** writing – review and editing.

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Conflicts of Interest

All co-authors, excluding A.M.K., are members of the MetabERN and AOA subnetwork. F.J.V.S. has received research grants, advisory board fees, and/or speaker's honoraria from Agios, Alexion, AlltRNA, Applied Pharma Research, Arla Food Int., Biomarin, Beatrix Research Fund, ESPKU, Nestle-Codexis Alliance, Moderna, Nutricia, NPKUA, NPKUV, Pluvia Biotech, PTC Therapeutics, Rivium Medical BV, Sobi, Tyrosinemia Foundation, Vitaflo, and ZONMW. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Supporting Information.

Appendix A

The TT1 MetabERN Professional Collaboration Group

The TT1 MetabERN professional collaboration group consists of:

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