2023

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Received: 30 January 2023 | Revised: 6 March 2023 | Accepted: 18 March 2023

DOI: 10.1002/ajmg.a.63195

AMERICAN JOURNAL OF medical genetics PART A WILEY

ORIGINAL ARTICLE

Development of informant-report neurobehavioral survey scales for PTEN hamartoma tumor syndrome and related neurodevelopmental genetic syndromes

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Abstract

There are few well-validated measures that are appropriate for assessing the full range of neurobehavioral presentations in PTEN hamartoma tumor syndrome (PHTS) and other neurodevelopmental genetic syndromes (NDGS). As potential therapeutics

Funding information
ADNP Kids Research Foundation; Autism Speaks; Malan Syndrome Foundation; PTEN Research; Simons Foundation Autism Research Initiative; SYNGAP Research Fund

are developed, having reliable, valid, free, and easily accessible measures to track a range of neurobehavioral domains will be crucial for future clinical trials. This study focused on the development and initial psychometric evaluation of a set of freely available informant-report survey scales for PHTS—the Neurobehavioral Evaluation Tool (NET). Concept elicitation, quantitative ratings, and cognitive interviewing processes were conducted with stakeholders and clinician–scientist experts, used to identify the most important neurobehavioral domains for this population, and to ensure items were appropriate for the full range of individuals with PHTS. Results of this process identified a PHTS neurobehavioral impact model with 11 domains. The final NET scales assessing these domains were administered to a sample of 384 participants (median completion time = 20.6 min), including 32 people with PHTS, 141 with other NDGS, 47 with idiopathic neurodevelopmental disorder (NDD), and 164 neurotypical controls. Initial psychometric results for the total scores of each scale indicated very good model ($\omega = 0.83–0.99$) and internal consistency reliability ($\alpha = 0.82–0.98$) as well as excellent test–retest reproducibility at 1-month follow-up ($r = 0.78–0.98$) and stability at 4-month follow-up ($r = 0.76–0.96$). Conditional reliability estimates indicated very strong measurement precision in key score ranges for assessing PHTS and other people with NDGS and/or idiopathic NDD. Comparisons across domains between PHTS and the other groups revealed specific patterns of symptoms and functioning, including lower levels of challenging behavior and more developed daily living and executive functioning skills relative to other NDGS. The NET appears to be a reliable and potentially useful tool for clinical characterization and monitoring of neurobehavioral symptoms in PHTS and may also have utility in the assessment of other NDGS and idiopathic NDD. Additional validation work, including convergent and discriminant validity analyses, are needed to replicate and extend these observations.

KEYWORDS
ADNP, Measure, Neurobehavioral, NFIX, PTEN, SYNGAP1

1 | INTRODUCTION

The last two decades have brought increasing recognition of the variety of clinical manifestations in individuals with germline heterozygous *PTEN* mutations (Eng, 2003; Hansen-Kiss et al., 2017; Yehia et al., 2019)—hereafter, PTEN hamartoma tumor syndrome (PHTS). PHTS is now broadly conceived to include individuals with classic Cowden and Cowden-like syndromes, Bannayan–Riley–Ruvalcaba Syndrome, Proteus and Proteus-like syndromes, and PTEN-related neurodevelopmental disorders (carrying a germline *PTEN* mutation). Recent investigations have uncovered a broad and diverse spectrum of neurocognitive dysfunction in individuals with PHTS (Busch et al., 2013, 2019; Frazier et al., 2015). This pattern ranges from no significant neurocognitive deficits or mild frontal-subcortical dysfunction to broader and more severe neurodevelopmental (NDD) and neuropsychiatric (NPD) disorders, including autism spectrum disorder (ASD) and/or intellectual disability (ID) (Frazier, 2019). Furthermore, a significant proportion of individuals with PHTS without a formal NDD diagnosis nevertheless show neurobehavioral alterations, including internalizing and externalizing psychopathology along with working memory, impulse control, and motor deficits (Balci et al., 2018; Busch et al., 2013, 2019).

Animal and human studies are beginning to uncover the underlying molecular and cellular changes associated with germline heterozygous *PTEN* mutations, including canonical dysregulation of PI3K/AKT and ERK/MAPK pathways and their impact on brain development and function (Fraser et al., 2004; Kwon et al., 2006; Kwon et al., 2003; Planchon et al., 2008; Song et al., 2018; Tilot et al., 2014; van Diepen & Eickholt, 2008; Weng, Brown, et al., 2001; Weng, Smith, et al., 2001), but also alterations in metabolic and other noncanonical pathways (Chen et al., 2018; He et al., 2015; Hobert et al., 2014; Pal et al., 2012). These studies are generating novel molecular treatment targets for a personalized medicine approach to PHTS intervention. Recently, a pilot randomized, controlled trial of everolimus, an mTOR

inhibitor, was completed in children and adults with PHTS and NDD (Hardan et al., 2021; Srivastava et al., 2022). This trial demonstrated safety of the everolimus dosing strategy and possible efficacy signals. However, in designing this study, investigators noted the lack of validated outcome measures appropriate for people with PHTS. This is a major hindrance to future longitudinal studies and clinical trials. Research efforts in PHTS would benefit from a neurobehavioral evaluation tool (NET) that complements clinic-based data collection (de Vries et al., 2018). Furthermore, clinical evaluation of PHTS suffers from lack of standardization or consistent measurement, in spite of the aforementioned complex and diverse spectrum of neurobehavioral impairments. Thus, if developed and validated, neurobehavioral instruments for PHTS could be implemented in clinical practice to screen for functional deficits and monitor change through development.

Unfortunately, at present, there are no available measures specifically designed for rapid and repeated evaluation of multiple neurobehavioral domains important in PHTS. The heterogenous PHTS clinical phenotype and pronounced variability and interplay between NDD and NPD symptoms, cognitive processing, and adaptive functioning present a particular assessment challenge. For instance, a recent study found that individuals with PHTS exhibited highly variable but significantly elevated levels of restricted and repetitive behaviors (RRB), regardless of the primary diagnosis (e.g., presence or absence of ASD) and cognitive functioning level (Uljarevic et al., 2021b). Levels of RRB and other clinical symptoms, including anxiety, have also been linked to difficulties in executive functioning in PHTS (Uljarevic et al., 2021a), emphasizing the need for simultaneous assessment of multiple domains. Further supporting the need for broad neurobehavioral evaluation, a recent study using a cross-measure approach has demonstrated high prevalence as well as significant individual differences in concurrent psychiatric symptoms among children and adolescents with PHTS (Steele et al., 2021), with a significant negative impact on affected individuals and their families (Macken et al., 2019).

A number of instruments have been developed to assess neurobehavioral symptoms and functional deficits commonly seen in PHTS, including measures of ASD (e.g., Social Responsiveness Scale-2 [SRS-2]; Social Communication Questionnaire [SCQ]); internalizing, externalizing and general behavioral problems (e.g., Behavior Assessment System for Children, 3rd Edition [BASC-3]; Child Behavior Checklist [CBCL]; Strengths and Difficulties Questionnaire [SDQ]); adaptive skills (e.g., Vineland Adaptive Behavior Scales [VABS]) and executive functioning (e.g., Behavior Rating Inventory of Executive Functioning [BRIEF]). However, these measures present with a range of limitations in the context of PHTS. First, existing survey tools tend to evaluate a single broad construct (e.g., SRS-2) or a subset of relevant behaviors (e.g. Aberrant Behavior Checklist [ABC]), thus necessitating the use of many instruments. This can make caregiver-report batteries onerous, increasing rater fatigue, reporting biases, and participant dropout. In a recent large-scale neurobehavioral study of PHTS, the parent-report instrument battery required 105 min to complete using published administration times (Busch et al., 2019). Further, currently available instruments were not constructed to assess the full range of functional presentations, are less relevant for certain ages or cognitive levels, might exclude some cases due to item wording (e.g., SRS-2 verbal items in nonverbal people), and were normed as separate instruments on healthy and/or idiopathic NDD populations. Importantly, none of the existing instruments were developed specifically for people with PHTS or other neurodevelopmental genetic syndromes (NDGS) and, therefore, might show diminished psychometric properties and/or a different factor structure in these unique populations (Sansone et al., 2012). Finally, the most widely used measures for characterizing neurobehavior are commercial instruments with no or limited online administration capability that significantly limits access and use in large-scale clinical and research efforts with a geographically diverse rare genetic syndrome.

The primary aim of the present study was to develop a PHTS neurobehavioral impact model and an associated set of online-administered informant-report (parent or other close relationship) survey scales, hereafter called the neurobehavioral evaluation tool (NET). Given the diverse and heterogeneous clinical and cognitive profiles of people with PHTS and the need for multiple endpoints that can be tracked regularly, NET scales were developed to be brief while retaining appropriate content coverage. The development of brief scales avoids burdensome data collection, particularly on already stressed caregivers, and reduces the likelihood of patient attrition in clinical trials and longitudinal observational studies. NET scale development followed best-practice recommendations and included the involvement of parent and patient stakeholders, in addition to clinical experts, to identify the most crucial neurobehavioral areas to evaluate. The neurobehavioral impact model and scale development processes used both qualitative and quantitative methods to identify neurobehavioral domains and content areas, including concept elicitation interviews, quantitative domain and content area importance ratings, and cognitive interviews. This approach ensures that measures assess constructs that are meaningful to patient and family functioning while also covering a breadth of clinical presentations across age/development, cognitive and language levels, and behavioral presentations. Given that a range of NDD and NPD symptoms and broad spectra of cognitive processing and adaptive functioning abilities and deficits are also commonly observed across other neurodevelopmental genetic syndromes (NDGS), parents and clinician–scientist experts from other NDGS were also included in the development process for the NET scales to evaluate whether the NET has the potential to advance insights and clinical practice in these populations as well.

After NET survey scales were developed, a secondary aim of this study was to conduct initial psychometric evaluation of these measures in PHTS, other NDGS, idiopathic NDD, and neurotypical controls. Initial evaluation included estimation of prior specified factor models, scale and conditional reliability, and test–retest reproducibility (1-month follow-up) and stability (4-month follow-up). Finally, using baseline NET data, exploratory analyses examined the pattern of neurobehavioral symptoms and functioning in PHTS relative to other NDGS and idiopathic NDD.

2 | METHODS

The NET development process is outlined in Figure 1. Briefly, this included an a priori PHTS neurobehavioral impact model with 20 domains and 116 content areas (Appendix S1) developed based on review of the existing literature, clinical experiences with PHTS patient evaluations and systematic review of existing instruments (Appendix S2), concept elicitation, and quantitative rating processes. Once the final conceptual model was developed, further processes included item writing and evaluation, development of instruction sets and rating frames/response scales, and cognitive interviewing.

2.1 | Concept elicitation process

Concept elicitation methods were developed in conjunction with Adroit Research and closely followed the methods of a recent impact model study for ASD (McDougall et al., 2018). Twelve participants were recruited with assistance from the PTEN Foundation, including three individuals with PHTS and nine parent informants (Appendix S3). The involvement of 12 participants in this phase was deemed sufficient based on prior research (Guest et al., 2006). Separate semi-structured interviews were developed for people with PHTS and informants with each based on the a priori neurobehavioral model, covering all 20 neurobehavioral domains (e.g., "Does [insert name] ever engage in self-injurious behaviors") as well as evaluation of the meaningfulness of change of any identified impacts (e.g., "What areas that you have identified are most important to see improve or change?"; see Appendix S4). Each participant completed a video-recorded interview conducted via Zoom with the research coordinator. Participants were encouraged to elaborate on responses to questions and to articulate any impacts they, their family, and/or their child with PHTS experienced. The minimum length interview was 37 min and the maximum length interview was 85 min (median

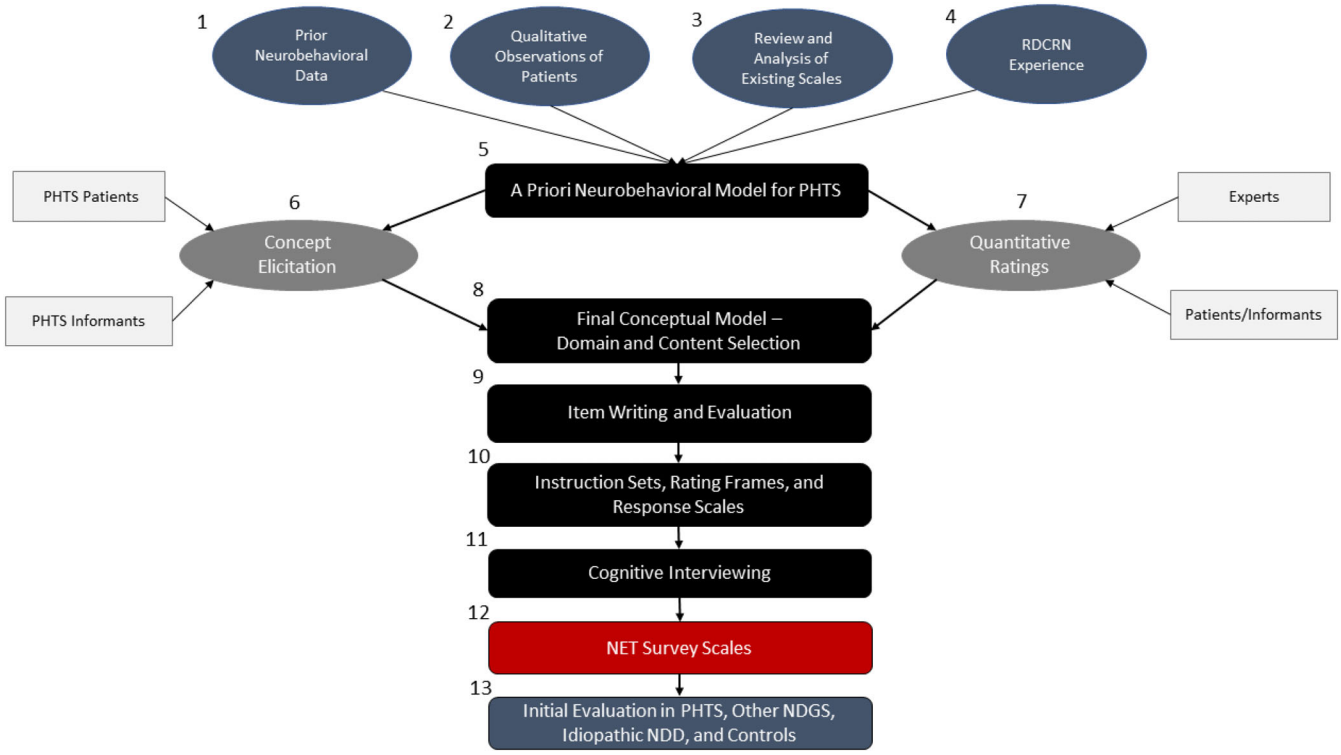

FIGURE 1 NET Development Process. NET development process steps included: Review of published data from peer-reviewed studies of neurobehavioral function in people with PTEN Hamartoma Tumor Syndrome (PHTS) (1), qualitative data from observations during neuropsychological evaluations of people with PHTS (2), review and analysis of existing neurobehavioral scales as a part of the UOM-20-001 project (Principal Investigators: Mirko Uljarević, MD, PhD & Antonio Y. Hardan, MD; Co-Investigator: Thomas W. Frazier, PhD) (3), and experience with the battery development and test administration within the NIH-funded (1U54NS092090) Rare Disease Clinical Research Network-Developmental Synaptopathies Consortium (RDCRN-DSC) (4). This information was used to develop an a priori neurobehavioral impact model for PHTS (5). Using this a priori model, qualitative data was collected using concept elicitation interviews of people with PHTS and informants ($n = 13$); quantitative data from individuals with PHTS ($n = 6$) and clinician–scientist experts ($n = 6$); development of the final conceptual PHTS neurobehavioral impact model, including domain and content selection; item writing and evaluation; development of instruction sets, rating frames, and response scales for each survey measure; and cognitive interviews undertaken to elucidate how informants interpreted each item. The end result of this process was the 11 initial NET informant-report survey scales. As a final step for this study, data were collected from people with PHTS, other neurodevelopmental genetic syndromes (NDGS), idiopathic neurodevelopmental disorders, neurotypical siblings, and unrelated healthy controls. NDGS, neurodevelopmental genetic syndromes; NDD, neurodevelopmental disorder; PHTS, PTEN hamartoma tumor syndrome.

length = 67 min, mean length = 64 min, standard deviation [SD] length = 11.9 min). Five raters were trained and supervised in the extraction and coding process. Extracted statements included any sentences or phrases that describe strengths, weakness, or challenges faced by the people with PHTS, currently or in the past. After statements were coded, negatively-valenced (impact) statements were summed within neurobehavioral domains and content areas. To evaluate concept occurrence and saturation, domain and content area sums were converted to present/absent (0/1) codes and these codes were evaluated across sets of three participants representing successive quarters of the sample.

2.2 | Quantitative rating process

Using the a priori PHTS neurobehavioral model, six PHTS clinician–scientist experts, six PHTS caregiver-informants, six clinician–scientist experts in other NDGS (ADNP, SYNGAP1, NFIX, and SCN2A) and/or idiopathic NDD, and four caregiver-informants for other NDGS (ADNP, SYNGAP1, and NFIX) and/or idiopathic ASD were asked to complete two surveys designed to identify the most important neurobehavioral domains and content areas to include in the NET. Key survey questions elicited ratings of overall value and importance of each domain and content area using a 0 (not at all important) to 100 (extremely important) slider scale. See Appendix S5 for additional details. Agreement between PHTS experts and patients/informants was examined using an intraclass correlation coefficient evaluating absolute agreement (Shrout & Fleiss, 1979).

2.3 | Development of the final PHTS neurobehavioral impact model

The final conceptual model was developed by combining findings from the concept elicitation and quantitative rating processes. Specifically, to be retained, neurobehavioral domains had to show at least moderate to high occurrence and saturation within the concept elicitation process and were at least moderately rated (>70) by either PHTS experts or caregiver-informants.

2.4 | Item writing, response scales, and rating frames

Detailed process of item writing and choice of response scales rating frames is described in Appendix S6. Items were written to be brief, to avoid conflating multiple constructs or processes, for at least three items to be included for each domain, and to use plain language with examples or qualifiers when needed. Where possible, phrase content from the concept elicitation process was used to inform item writing. Instruction sets were written to briefly convey the essential information for the completion of each item, the rating frame, and an introduction to the response scale. Rating frames were generally 1-2-week time periods for domains that are frequently observed (Attention Deficit/Hyperactivity Disorder [ADHD] symptoms, executive functioning, anxiety, irritability, depression). A one-month timeframe was used for mania, sleep, social communication, restricted/repetitive behavior, and challenging behavior to allow for a sufficient observation period to capture the behavior and to avoid overemphasizing transient difficulties. Daily living and motor skills were rated based on the patient's current level of function. Five-point Likert scales focused on frequency or severity were used for most scales. The exceptions were the daily living skills and motor skills scales, which used 4-point Likert scales to avoid overuse of a neutral response, and the quality of life scale, which used 5-point Likert scales focused on agreement with each statement. Experts, caregiver-informants, and patients provided feedback on each item. Items were excluded or revised based on this feedback.

2.5 | Cognitive interviewing

After the initial NET scales were developed, seven PHTS caregiver-informants participated in a hybrid "think aloud" and "probe questions" cognitive interviewing method to better understand how they understood each scale and items and how they formulated their ratings for each item (Ryan et al., 2012). See Appendix S7 for additional cognitive interviewing details and Appendix S8 for the final NET survey scales.

2.6 | Participants for initial scale evaluation

Study groups included PHTS, ADNP, SYNGAP1, and NFIX patients recruited via contacts through the PTEN Foundation with the support of the PTEN Research Foundation, the ADNP Kids Foundation, the SYNGAP Research Fund, and the Malan Syndrome Foundation. Other NDGS patients were recruited via the Simons Foundation Searchlight portal and included people with mutations in GRIN2B ($n = 11$), CSNK2A1 ($n = 13$), HIVEP2 ($n = 8$), SCN2A ($n = 8$), MED13L ($n = 6$), and STXBP1 ($n = 10$). Given the relatively small sample sizes for ADNP ($n = 13$) and these groups, they were combined into a single "other NDGS" group. Individuals were included if they were between the ages of 3 and 45 at enrollment and had an available parent or other close relative/caregiver to complete NET scales. Siblings of NDGS patients were also eligible to participate and unrelated controls were recruited using StudyKik, a national recruitment service. Siblings and unrelated controls who were reported to have an idiopathic neurodevelopmental disability were included in a separate group. Participants were predominantly from the US ($n = 335$, 88%), but a small minority of participants with informants fluent in English were also included from other countries (United Kingdom $n = 14$, $n =$ Canada $n = 25$, Australia $n = 4$, New Zealand $n = 1$, Ireland $n = 2$, Netherlands $n = 1$, Norway $n = 1$, Israel $n = 1$).

2.7 | NET administration

Parent/caregiver informants completed a demographic and clinical information questionnaire (Appendix S9) followed by each of the NET scales at baseline, 1-month, and 4-month follow-up timepoints. The survey was completed using the Qualtrics-XM platform.

IRB approval was obtained for all of the qualitative and quantitative procedures of the study, including administration of the final NET scales, and parents/legally-authorized representatives and adult patients provided informed consent prior to completing any study procedures. Assent for minors was also obtained, where appropriate.

2.8 | Statistical analyses

2.8.1 | Sample characterization

Descriptive statistics for demographic and clinical factors were computed to characterize the sample and Chi-square or univariate ANOVA were used to compare across the seven study groups (PHTS, SYNGAP1, NFIX, other NDGS, idiopathic NDD, sibling controls, and unrelated healthy controls).

2.8.2 | Scale factor structure

To determine the factor structure of each NET survey scale, exploratory structural equation model (ESEM) solutions with and without a general bifactor were fit for each scale, with the exception of the daily living skills scale where only a single ability gradient was anticipated based on prior analyses of similar scales (de Bildt et al., 2005). ESEM models were based on the a priori scale construction and content analyses. ESEM models were first fit in the baseline data and then again in the 1-month and 4-month follow-up data to evaluate within-sample replication of the initial factor structure over time. Given that NET scale development focused on brief scales with adequate but not extensive content coverage, extraction of specific factors was done to identify the best fitting factor solution, with the understanding that many specific factors may be poorly identified and/or have weaker measurement properties, limiting their utility. Thus, the focus of subsequent psychometric analyses was on the total scale score represented by the general bifactor.

2.8.3 | Reliability

Scale reliability (internal consistency) was calculated using Cronbach's alpha (α) (Streiner & Norman, 1995). Model (factor) reliability was calculated using MacDonald's omega (ω) derived from the bifactor ESEM solution (Rodriguez et al., 2016). Conditional reliability was estimated using item response theory (IRT) analyses (Embretson & Reise, 2000). Reliability estimates falling in the ranges 0.70 to 0.79, 0.80–0.89, and >0.90 were considered fair, good, and excellent (Nunnally & Bernstein, 1994), respectively. Test–retest reproducibility (one-month follow-up) and stability (4-month follow-up) were estimated using Pearson's bivariate correlations.

2.8.4 | Neurobehavioral patterns in PHTS and other NDGS/NDD groups

To explore unique patterns of neurobehavioral function in PHTS and other NDGS/NDD groups, NET scales were first normed using regression-based norming in unrelated healthy controls, with age, age^2 (to capture nonlinear developmental trends), and sex included as predictors in each equation. This approach puts each NET scale score on a z-score metric relative to healthy controls. Using these standardized residual scores, univariate analysis of variance models were computed, with each of the seven groups as the independent variable and the NET survey scale total scores as the dependent variables in separate analyses.

2.8.5 | Statistical power

Factor analyses were expected to be adequately powered for each scale given the number of items per scale and a total sample size >350 (Wolf et al., 2013). Assuming total sample sizes of 200+ for reliability analyses and test–retest data, statistical power to detect a bivariate correlation of $r \geq 0.40$ was excellent (>0.99; one-tailed p-value of 0.05). Power to detect group differences across NET scales, assuming a minimum sample size of 23, was at least adequate (>0.81) if large group differences were observed ($d \geq 0.80$; $\alpha = 0.05$, two-tailed). For larger group sizes ($n > 40$), power was adequate, even for medium effects ($d \geq 0.50$).

3 | RESULTS

3.1 | Concept elicitation

Concept codes showed acceptable to good reliability for both domains and content areas (Appendix S10). Concept saturation for neurobehavioral domains was achieved by the fifth participant interview, and 18 of the 20 domains showed clear evidence of saturation (Appendices S11 and S12). For content areas, concept saturation appears to be adequately achieved by the 11th participant interview, and 72 content areas showed clear evidence of saturation with 43 content areas endorsed by at least 25% of participants (Appendices S13 and S14). The final concept map is displayed in Appendix S15.

3.2 | Quantitative ratings

PHTS expert and patient/informant domain importance ratings indicated moderate to high agreement (ICC(2,2) = 0.59, $p = 0.001$). Personality/temperament, GI problems, thought disorder, and visual

perceptual skills were consistently rated lower in importance, while speech/language, quality of life, and anxiety were consistently rated as being of very high importance (Appendix S16). Interestingly, PHTS and other NDGS/NDD experts showed strong correspondence in importance ratings across their respective conditions (ICC(2,2) = 0.74, $p < 0.001$), as did PHTS and NDGS/NDD patients/informants (ICC (2,2) = 0.65, $p = 0.012$). Qualitative feedback indicated that speech/language, memory, visual perceptual skills, and seizures might be de-emphasized given the availability of objective measures. Each domain had at least one moderate to highly rated content area (>70 out of 100; Appendices S17 and S18).

3.3 | Final PHTS neurobehavioral impact model

The final impact model comprised 11 domains, including 9 neurobehavioral constructs and 2 domains representing impacts of neurobehavioral deficits (Figure 2). Domains with high occurrence and saturation from the concept elicitation process, moderate to high importance ratings, without concerns regarding being age-dependent or being more appropriately measured objectively, were retained. The only exception was RRB which was retained based on clinician–scientist input, given that it is a key feature of ASD, a common developmental diagnosis in PHTS (Appendix S19). Six scales were keyed so that higher scores indicated greater symptoms/problems (Anxiety, Challenging Behavior, Mood, ADHD, RRB, and Sleep), and five scales were keyed so that higher scores indicated greater skills/functioning or quality of life (daily living skills, social communication/interaction, motor skills, executive functioning, and quality of life).

3.4 | Sample characteristics for initial evaluation

On average, participants were younger in the NFIX and SYNGAP1 groups and older in the PHTS and idiopathic NDD groups, with high rates of spousal informants in the latter groups. All groups had very high proportions of White/Caucasian participants, although Hispanic ethnicity met or exceeded US population proportions in most groups and the sample had a wide range of household incomes. Not surprisingly, estimated cognitive levels were substantially lower in the NFIX, SYNGAP1, and other NDGS groups and to a less extent in the PHTS group relative to control groups. Informant-reported developmental diagnoses were highly variable across NDGS groups, but with elevated rates of ASD, ID/Global Developmental Delay (GDD), anxiety, and motor disorder reported, particularly in NFIX, SYNGAP1, and other NDGS groups. Of the 384 participants, the majority had follow-up data at 1-month ($n = 283$, 74%) and 4-months ($n = 206$, 54%) post-baseline, with slightly better follow-up in NDGS and idiopathic NDD groups (1-month $n = 178$, 81%; 4-month $n = 131$, 60%) (Table 1).

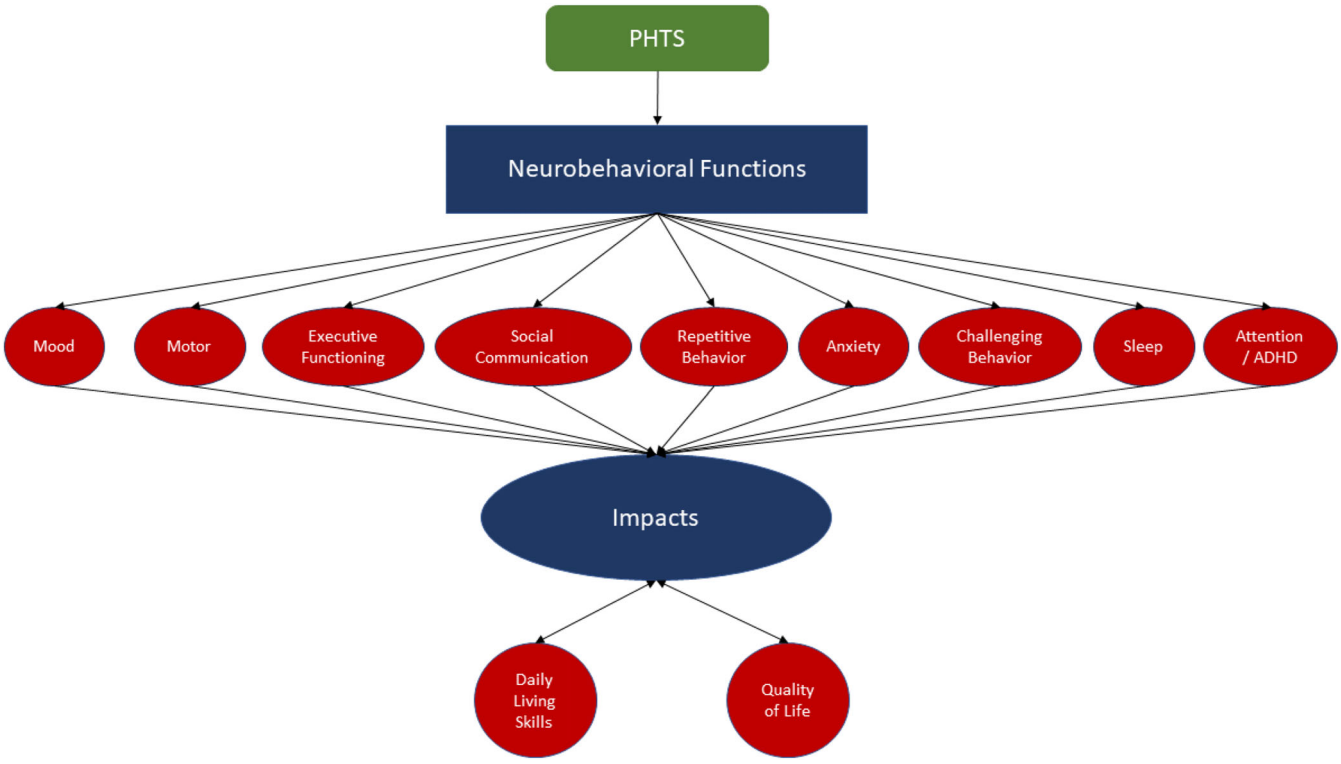

FIGURE 2 PTEN hamartoma tumor syndrome (PHTS) neurobehavioral impact model. Individuals with PHTS have highly variable neurobehavioral function that, when impaired, can lead to significant impacts on individual and family functioning. This final concept model served as the basis for the development of NET informant-report survey scales. Reciprocal relationships from functional impacts back to neurobehavioral impacts are possible but not shown. ADHD, attention-deficit/hyperactivity disorder; PHTS, PTEN hamartoma tumor syndrome.

TABLE 1 Demographic and clinical characteristics by study group.

	Sibling controls	Unrelated controls	PHTS	NFIX	SYNGAP1	Other NDGS	NDD	χ^2/F(*p*)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	
N	41	123	32	23	49	69	47	
Informant age (M, SD)	43 (6)	42 (9)	43 (8)	40 (10)	43 (8)	43 (7)	42 (8)	0.6 (0.713)
Informant sex (% female)	38 (93%)	101 (82%)	28 (88%)	20 (87%)	45 (92%)	67 (97%)	43 (92%)	13.2 (0.353)
Informant relationship to Participant								33.6 (0.014)
Biological parent	40 (98%)	107 (87%)	25 (78%)	22 (96%)	44 (90%)	66 (96%)	37 (79%)	
Adoptive or custodial parent	0 (0%)	3 (2%)	1 (3%)	1 (4%)	3 (6%)	2 (3%)	2 (4%)	
Other biological relative/sibling	1 (2%)	6 (5%)	0 (0%)	0 (0%)	1 (2%)	1 (1%)	2 (4%)	
Spouse/other non-biological relative	0 (0%)	7 (6%)	6 (19%)	0 (0%)	1 (2%)	0 (0%)	6 (13%)	
Household Income (USD)								70.4 (0.019)
<$25,000	1 (2%)	6 (5%)	0 (0%)	0 (0%)	0 (0%)	3 (4%)	7 (15%)	
$25,000–$34,999	2 (5%)	8 (7%)	0 (0%)	1 (4%)	2 (4%)	3 (4%)	2 (4%)	
$35,000–$49,999	2 (5%)	6 (5%)	1 (3%)	3 (13%)	3 (6%)	3 (4%)	4 (9%)	
$50,000–$74,999	7 (17%)	18 (15%)	9 (28%)	4 (17%)	5 (10%)	6 (9%)	10 (21%)	
$75,000–$99,999	2 (5%)	24 (20%)	4 (13%)	3 (13%)	4 (8%)	9 (13%)	1 (2%)	
$100,000–$149,999	8 (20%)	27 (22%)	7 (22%)	4 (17%)	12 (25%)	14 (20%)	10 (21%)	
$150,000–$199,999	5 (12%)	16 (13%)	4 (13%)	5 (22%)	10 (20%)	5 (7%)	5 (11%)	
$200,000+	6 (15%)	14 (11%)	2 (6%)	2 (9%)	9 (18%)	12 (17%)	4 (9%)	
Did not report	8 (20%)	4 (3%)	5 (16%)	1 (4%)	4 (8%)	14 (20%)	4 (9%)	
Participant age (M, SD)	12 (5)	12 (8)	16 (14)	9 (7)	10 (7)	11 (6)	15 (9)	3.4 (0.003)
Participant sex (% female)	24 (59%)	55 (55%)	20 (38%)	12 (48%)	28 (43%)	31 (55%)	31 (34%)	11.1 (0.086)
Participant race/ethnicity								
White/Caucasian	38 (93%)	99 (81%)	29 (91%)	23 (100%)	42 (86%)	65 (94%)	41 (87%)	13.3 (0.038)
Black/African American	2 (5%)	10 (8%)	0 (0%)	0 (0%)	7 (14%)	3 (4%)	7 (15%)	12.8 (0.046)
Middle Eastern or North African	2 (5%)	1 (1%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9.2 (0.160)
East Asian	2 (5%)	11 (9%)	3 (9%)	0 (0%)	2 (4%)	5 (7%)	0 (0%)	7.6 (0.268)
South Asian	2 (5%)	8 (7%)	0 (0%)	0 (0%)	1 (2%)	3 (4%)	0 (0%)	7.3 (0.289)
Native American/Alaskan Native	0 (0%)	3 (2%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	1 (2%)	4.9 (0.556)
Native Hawaiian/Pacific Islander	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2.1 (0.908)
Hispanic	7 (17%)	20 (16%)	1 (3%)	5 (22%)	9 (18%)	3 (4%)	10 (21%)	16.6 (0.167)
Unknown	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4.3 (0.641)
Did not report	0 (0%)	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	3.9 (0.688)

TABLE 1 (Continued)

	Sibling controls	Unrelated controls	PHTS	NFIX	SYNGAP1	Other NDGS	NDD	χ^2/F(*p*)
Cognitive level (informant estimated)								343.9 (<0.001)
Very high or above (120+)	5 (12%)	14 (11%)	3 (9%)	0 (0%)	0 (0%)	1 (1%)	9 (19%)	
High Average (110–119)	19 (46%)	61 (50%)	5 (16%)	0 (0%)	0 (0%)	0 (0%)	16 (34%)	
Average (90–109)	14 (34%)	44 (36%)	15 (47%)	0 (0%)	3 (6%)	2 (3%)	17 (36%)	
Below average (80–89)	0 (0%)	0 (0%)	1 (3%)	2 (9%)	4 (8%)	8 (12%)	2 (4%)	
Borderline impairment (70–79)	0 (0%)	0 (0%)	1 (3%)	2 (9%)	1 (2%)	3 (4%)	0 (0%)	
Mild impairment (55–69)	0 (0%)	0 (0%)	1 (3%)	5 (22%)	7 (14%)	13 (19%)	3 (6%)	
Moderate impairment (40–54)	0 (0%)	0 (0%)	2 (6%)	9 (39%)	11 (22%)	17 (25%)	0 (0%)	
Severe impairment (21 to 39)	0 (0%)	0 (0%)	0 (0%)	2 (9%)	11 (22%)	12 (17%)	0 (0%)	
Profound impairment (<20)	0 (0%)	0 (0%)	0 (0%)	2 (9%)	6 (12%)	4 (6%)	0 (0%)	
Did not report	3 (7%)	4 (3%)	4 (13%)	1 (4%)	6 (12%)	9 (13%)	0 (0%)	
Cognitive estimate from prior testing	5 (12%)	20 (16%)	15 (47%)	13 (57%)	27 (55%)	31 (45%)	25 (53%)	66.5 (<0.001)
Developmental diagnoses (*n*, %)								
ASD	-	-	9 (28%)	5 (22%)	37 (76%)	31 (45%)	6 (13%)	46.0 (<0.001)
ID/GDD	-	-	11 (34%)	20 (87%)	44 (90%)	64 (93%)	1 (2%)	133.9 (<0.001)
Speech/language disorder	-	-	10 (31%)	10 (44%)	38 (78%)	45 (65%)	9 (19%)	44.0 (<0.001)
ADHD	-	-	5 (16%)	1 (4%)	6 (12%)	19 (28%)	23 (49%)	25.9 (<0.001)
ODD/CD	-	-	0 (0%)	1 (4%)	5 (10%)	2 (3%)	4 (9%)	5.8 (0.217)
Anxiety disorder	-	-	5 (16%)	7 (30%)	11 (22%)	10 (15%)	14 (30%)	5.7 (0.222)
Specific learning disorder	-	-	2 (6%)	0 (0%)	2 (4%)	3 (4%)	5 (11%)	4.2 (0.385)
Motor/coordination disorder	-	-	4 (13%)	6 (26%)	27 (55%)	21 (30%)	0 (0%)	41.4 (<0.001)
Depressive disorder	-	-	4 (13%)	0 (0%)	0 (0%)	0 (0%)	8 (17%)	23.4 (<0.001)
Bipolar disorder/mania	-	-	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (2%)	2.0 (0.745)
Obsessive compulsive disorder	-	-	0 (0%)	0 (0%)	4 (8%)	2 (3%)	1 (2%)	5.9 (0.204)
Tic disorder	-	-	0 (0%)	0 (0%)	2 (4%)	1 (1%)	1 (2%)	2.5 (0.644)
Feeding/eating disorder	-	-	0 (0%)	0 (0%)	11 (22%)	12 (17%)	0 (0%)	23.0 (<0.001)
1-Month Follow-Up Completed	29 (71%)	76 (62%)	31 (97%)	21 (91%)	37 (76%)	57 (83%)	32 (68%)	25.4 (<0.001)
4-Month Follow-Up Completed	25 (61%)	50 (41%)	29 (91%)	19 (83%)	28 (57%)	31 (45%)	24 (51%)	37.1 (<0.001)

Note: Non-ASD diagnoses do not sum to 100% because children could be diagnosed with more than one condition. Note that race/ethnicity categories are not mutually exclusive and participants were encouraged to select all options that apply. For statistical tests with low cell sizes, Fisher's exact test was also computed, but results were highly consistent with the chi-square analysis. For this reason, chi-square is reported with the associated *p* value.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ID/GDD, intellectual disability/global developmental delay; ODD/CD, oppositional defiant disorder/conduct disorder.

3.5 | Factor structure

Each NET scale showed strong evidence of a general factor (Table 2) at each timepoint. Bifactor models fit substantially better than corresponding correlated factors models. The first eigenvalues were 3–30 times larger than subsequent eigenvalues, often accounting for more than 50% of the total variance in items. Factor inter-correlations from correlated factors models (removing the bifactor) tended to be positive and medium-to-large in magnitude, supporting the existence of substantial common variance, consistent with a general factor.

With the exception of the Daily Living Skills scale, the remaining NET scales showed evidence of specific factors beyond the general bifactor, with 3–6 specific factors identified (Appendices S20 and S21). Model fit for bifactor ESEM models was excellent in the baseline sample and remained excellent in the 1-month and 4-month follow-up data.

3.6 | Reliability

Model and internal consistency reliability was good to excellent for all NET total scale scores ($\omega = 0.83–0.99$; $\alpha = 0.82–0.98$; Table 3) and internal consistency was highly comparable when examined only in individuals with PHTS. Conditional reliability was good to excellent (≥0.80) for all six NET symptom scales from low ($\theta = -1.0$) to very high ($\theta = +3.0$) scores (Appendix 22). Conditional reliability was good to excellent (≥0.80), ranging from very low ($\theta = -2.8$) to high average ($\theta = +1.0$) for four of the five NET functioning scales. For the QoL scale, conditional reliability was at least fair (≥0.70) in the range from very low ($\theta = -2.8$) to extremely high ($\theta = +4.6$) scores.

Test–retest reproducibility estimates were very high across all scales ($r = 0.78–0.98$) and only slightly lower for test–retest stability ($r = 0.76–0.96$), with the highest stability estimates for motor and daily living skills. Similar levels were observed when only NDGS patients were examined.

3.7 | Completion times

The median completion time for all 11 NET scales at baseline was 20.6 min (Mean = 24.5, SD = 14.9; 95% CI = 22.8–26.2).

3.8 | Group profiles across NET scales

Group differences were statistically significant across all NET scales (largest $p = 0.048$), except the Anxiety scale ($p = 0.358$) (Figure 3, Appendix S23). PHTS patients showed levels of anxiety, RRB, ADHD, and sleep that were only about 1SD above the control mean, and mood symptoms were consistent with levels in controls. Social communication/interaction, daily living skills, executive functioning, and quality of life levels tended to fall 1–2SD below the control mean, and motor skills fell more than 3SD below the control mean.

The most prominent remaining patterns across NDGS groups were: (a) highly elevated challenging behavior, RRB, and ADHD symptoms in NFIX, SYNGAP1, and other NDGS groups, with smaller elevations for anxiety and sleep problems; (b) low levels on NET functional scales indicating lower performance/functioning for all NDGS groups, with the most severe functional impairments tending to occur in SYNGAP1, followed by other NDGS and NFIX; (c) the general pattern of elevated symptoms and low skill levels in NDGS followed estimated cognitive levels, with a few notable exceptions such as lower ADHD, restricted/repetitive behavior, and sleep problems in NFIX than would be expected based on cognitive estimates; and (d) idiopathic NDD cases tended to have lower symptom levels and higher functioning levels relative to NDGS cases, with only mild elevations for ADHD and sleep problems and small reductions in executive functioning and quality of life. Taken together, these findings provide preliminary evidence of concurrent (known-groups) validity of NET scales.

4 | DISCUSSION

This paper described the development and preliminary psychometric validation of the neurobehavioral evaluation tool (NET)—a set of freely-available informant-report survey scales for individuals with PHTS and NDGS that can be administered online, supplementing information collected at clinical visits. To our knowledge, this is the first dedicated tool specifically developed to assess the full range of neurobehavioral presentations seen in individuals with PHTS and other NGDS. Findings presented in this initial validation demonstrated that the scales within the NET are psychometrically sound instruments, suggesting that NET might be a promising instrument for characterizing the full clinical and functioning spectra relevant for PHTS and other NGDS in research contexts. The measure might also have utility in clinical contexts if offered at minimal cost with automated administration, scoring, and reporting functions to reduce clinician burden. Indeed, the NET scales had clear factor structures, with strong evidence of a dominant general factor corresponding to each neurobehavioral domain. The scales also showed very good model, internal consistency, and conditional reliability, as well as excellent test–rest reproducibility. Crucially, in addition to capturing a broad range of key neurobehavioral presentations, the NET was considerably briefer (mean completion time ≅ 21 min) than the length of comparable instrument batteries that could be developed using existing measures to provide a similar content coverage.

The pronounced variability and complexity in the profiles of NDD and NPD symptoms, cognitive processing, and adaptive abilities seen in individuals with PHTS (Balci et al., 2018; Busch et al., 2013, 2019; Frazier et al., 2015; Frazier et al., 2021; Hansen-Kiss et al., 2017; Hobert et al., 2014; Steele et al., 2021; Uljarevic et al., 2021a, 2021b) and other NDGS (Agarwal et al., 2019; Arnett et al., 2018; Berryer et al., 2013; Jimenez-Gomez et al., 2019; Mulder et al., 2020; Parker et al., 2015; Rai et al., 2018) present a significant assessment challenge. Although a range of currently available and widely-used instruments have been developed to capture discrete clinical presentations

TABLE 2 Factor analysis results by survey scale.

NET scales	First/second eigenvalue	Factor structure (g = general, s = specific factors)	Factor intercorrelations (range of *r*)	Baseline fit			1-month follow-up fit			4-month follow-up fit		
				RMSEA	CFI	TLI	RMSEA	CFI	TLI	RMSEA	CFI	TLI
Symptoms												
ANX	11.2/1.8	1 g, 3 s	0.36–0.49	0.058	0.989	0.981	0.076	0.983	0.973	0.071	0.988	0.980
CB	11.1/1.5	1 g, 5 s	0.32–0.66	0.009	0.999	0.999	0.001	0.999	0.999	0.001	0.999	0.999
RRB	10.5/1.6	1 g, 4 s	0.25–0.72	0.051	0.995	0.989	0.049	0.996	0.992	0.057	0.995	0.989
ADHD	10.1/2.6	1 g, 4 s	0.24–0.68	0.067	0.994	0.988	0.056	0.996	0.992	0.079	0.993	0.985
Mood	11.7/2.3	1 g, 3 s	0.33–0.71	0.071	0.990	0.984	0.060	0.992	0.986	0.054	0.994	0.990
Sleep	5.6/1.9	1 g, 5 s	0.20–0.41	0.045	0.993	0.974	0.020	0.999	0.995	0.022	0.998	0.993
Skills/functioning												
SCI	11.9/2.0	1 g, 4 s	0.05–0.67	0.050	0.997	0.994	0.053	0.996	0.993	0.038	0.998	0.997
DLS	29.8/0.9	1 g	-	0.066	0.995	0.995	0.064	0.995	0.994	-	-	-
Motor	18.4/1.3	1 g, 3 s	0.23–0.77	0.022	0.999	0.999	0.043	0.998	0.998	0.039	0.999	0.998
EF	9.9/2.2	1 g, 4 s	0.39–0.61	0.044	0.998	0.996	0.045	0.998	0.995	0.062	0.997	0.994
QoL	7.9/2.9	1 g, 6 s	0.01–0.59	0.040	0.994	0.986	0.009	0.999	0.999	0.036	0.995	0.989

Note: Factor inter-correlations were derived from the optimal correlated factors model and the smallest factor inter-correlation was provided to show that specific factors are significantly positively related supporting use of a total scale score. The largest 90% CI for RMSEA was +/− 0.025. See Appendices S21 and S22 for information on specific factor interpretation and items with significant loadings for each NET scale.

Abbreviations: ADHD, attention-deficit/hyperactivity symptoms scale; ANX, anxiety scale, CB, challenging behavior scale, DLS, daily living skills scale, EF, executive functioning scale; Mood, mood problems scale; Motor, motor skills scale; SCI, social communication/interaction skills scale; Sleep, sleep problems scale; RRB, restricted, repetitive behavior scale; QoL, quality of life scale.

TABLE 3 Completion times and reliability metrics for all NET informant-report scales.

	# items	Time to complete (median seconds) [IQR]	Model reliability (MacDonald's ω)	Internal consistency (Cronbach's α)	Test–retest reproducibility (1-month f/up)	Test–retest stability (4-month f/up)	IRT theta range (reliability ≥0.70)
Symptoms							
ANX	20	89 [70]	0.94	0.94	0.85	0.83	−2.0 to +4.4
CB	17	69 [59]	0.94	0.94	0.94	0.92	−1.0 to +4.0
RRB	17	97 [82]	0.95	0.94	0.93	0.92	−1.6 to +3.4
ADHD	18	89 [61]	0.94	0.94	0.90	0.89	−2.5 to +3.3
Mood	20	86 [61]	0.93	0.93	0.78	0.76	−1.7 to +4.6
Sleep	15	72 [55]	0.83	0.82	0.82	0.78	−1.5 to +3.8
Skills/functioning							
SCI	20	120 [102]	0.95	0.95	0.88	0.88	−4.1 to +1.5
DLS	35	184 [154]	0.99	0.98	0.93	0.93	−3.0 to +2.0
Motor	23	94 [88]	0.98	0.97	0.98	0.97	−3.4 to +1.0
EF	18	83 [51]	0.94	0.93	0.94	0.93	−3.4 to +2.5
QoL	23	154 [102]	0.89	0.88	0.89	0.87	−1.8 to +4.6

Note: Theta range reflects the range of theta values for which reliability estimates remained at or above 0.70 indicating at least adequate reliability. Median from baseline to 1-month follow-up was 30 days [IQR = 15 days] and from baseline to 4-month follow-up was 115 days [IQR = 15]. Median completion time for all 11 scales was 20.6 min [IQR = 15 min].

Abbreviation: ANX, anxiety scale; ADHD = attention-deficit/hyperactivity symptoms scale; CB, challenging behavior scale; DLS, daily living skills scale; EF, executive functioning scale; IQR, interquartile range; IRT, item response theory; Mood, mood problems scale; Motor, motor skills scale; QoL, quality of life scale; RRB, restricted, repetitive behavior scale; Sleep, sleep problems scale; SCI, social communication/interaction skills scale.

in PHTS and other NGDS, including ASD, ADHD, internalizing and externalizing symptoms, these tools tend to evaluate either a single broad construct or only a subset of relevant symptoms or behaviors. Thus, the characterization of the full neurobehavioral profiles necessitates the use of a number of scales, resulting in significant participant burden and high rates of dropout when used in study designs requiring repeated administration (e.g., longitudinal natural history observational studies and clinical trials). Further, given that none of the currently existing instruments were specifically designed for individuals with PHTS and other NGDS, they do not capture the full range of functional and clinical presentations, in particular for certain ages or cognitive levels.

Given the noted limitations of the current instruments, there is an urgent need to assess the full clinical, cognitive, and adaptive functioning spectrum in people with PHTS for the purpose of clinical characterization and tracking change due to natural developmental progression or treatments. The NET scales were developed in response to this challenge, following gold standard principles for measurement development (Boateng et al., 2018; Center for Drug Evaluation and Research, 2009). The development process combined qualitative and quantitative methods, including the involvement of parent and patient stakeholders, to identify the most crucial neurobehavioral domains and content areas. The resultant conceptual model included 9 neurobehavioral constructs (mood, motor functioning, executive functioning, social communication, restricted/repetitive behaviors, anxiety, challenging behaviors, sleep and attention/ADHD) and two domains representing the impacts of neurobehavioral deficits (quality of life, and daily living skills).

A series of exploratory structural equation models identified that while the unidimensional model provided the best fit for the Daily Living Skills scale, the other 10 scales showed evidence of specific factors beyond the general bifactor. This demonstrates that, despite being developed with brevity in mind, the NET scales showed at least adequate coverage that will enable detailed clinical research characterization. More specifically, the Social and Communication scale comprised of perspective taking, affiliation, nonverbal communication, and inappropriate interaction factors; the RRB scale of repetitive sensory motor, insistence on sameness, sensory sensitivity, and restricted interests factors; ADHD scale of inattention, hyperactivity, impulsivity and disorganization factors; Mood scale of irritability, hypomania and depression factors; Anxiety scale of worry, separation and social anxiety factors; Challenging Behaviors Scale of aggression, property destruction, elopement, conduct problems, and self-injury factors; Sleep scale of nighttime waking, bedtime resistance, difficulty falling/staying asleep, and difficulty waking factors; Motor Scale of basic gross motor, fine motor, and strength factors; the Executive Functioning scale of sequencing, processing speed, emotion regulation, and risk avoidance factors; and QoL scale of financial, close support, community support, family, physical and mental health, and change in QoL factors. Importantly, model fit for bifactor ESEM models was excellent in the baseline sample and remained excellent in the 1-month and 4-month follow-up data, suggesting that these factors are likely to replicate in independent samples.

Classical test theory and IRT reliability indicators were strong across all NET scales. More specifically, model and internal consistency reliability were good to excellent for all NET total scale scores.

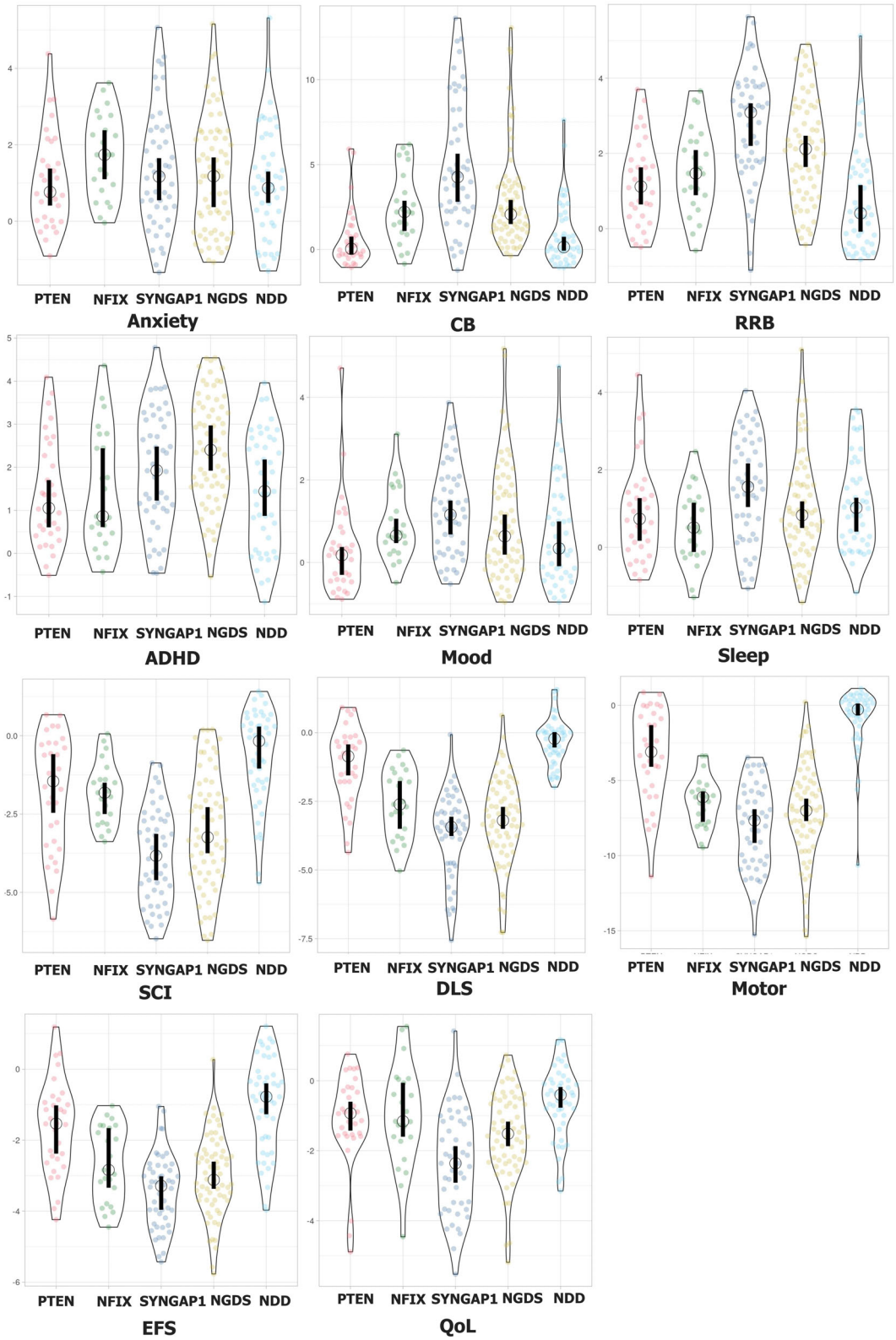

FIGURE 3 PHTS and other NDGS group differences across NET survey scales. ADHD, attention-deficit/hyperactivity disorder; CB, challenging behavior; DLS, daily living skills; EFS, executive functioning scale; RRB, restricted/repetitive behavior; SCI, social communication/interaction; QoL, quality of life.

Further, conditional reliability was good to excellent for all six NET symptom scales from low to very high scores and from very low to high average scores for 4 of the 5 NET functioning scales. For the Quality of Life scale, conditional reliability was at least fair from low to extremely high scores. This indicates that the NET scales are accurately identifying individual differences in key ranges that will be

crucial for future longitudinal studies, where sensitive measurement of change is paramount. Test–retest reproducibility and stability estimates were very high across all scales, indicating that changes in NET scales are not likely to be a function of measurement error and increasing the likelihood changes in each measure's total score reflect real differences in parent/informant perceptions of neurobehavioral function. It will be important to test stability over a longer time interval to ensure an adequate balance of stability and sensitivity to change. If sensitivity to change is demonstrated, the brevity of the NET might allow for more frequent assessements in the context of intervention studies, thereby increasing statistical power and reducing the sample size needed for clinical trials.

Finally, the present results provide preliminary evidence of concurrent validity of NET scales. For instance, individuals with PHTS showed elevated anxiety, restricted/repetitive behavior, ADHD, and sleep symptom levels (approximately 1 SD above the control mean), and reduced levels of social communication/interaction, daily living skills, executive functioning, and quality of life (1–2 SD below the control mean) and motor skills (more than 3 SD below the control mean). Of note, specific NGDS showed somewhat distinct patterns of strengths and weakness across specific domains captured by the NET scales. For example, inividuals with NFIX showed lower ADHD, restricted/repetitive behavior, and sleep problems than would be expected based on cognitive estimates. When compared to NGDS cases, idiopathic NDD cases tended to have lower symptom levels and higher functioning levels. Thus, the NET scales are not only likely to be useful for capturing neurobehavioral functions and impacts in PHTS but may be helpful for understanding individual differences and group differences in other NDGS.

Several limitations of the current study warrant mention. PHTS, SYNGAP1, NFIX, and other NDGS included in this study have a low prevalence. While our power analysis indicated at least adequate power for group comparisons and psychometric analyses were well powered in the full sample, our current data should nevertheless be treated as preliminary and studies with larger group sample sizes should be completed to replicate our findings. Relatedly, sample size precluded us from testing invariance across specific clinical groups as well as across specific cognitive and demographic characteristics. Thus, it will be important to conduct measurement invariance tests as further data is collected. An additional limitation of this study was a reliance on informant reports, including cognitive levels and symptom severity estimates. Given the online nature of the research coupled with low local prevalence of NDGS conditions, it was not feasible to conduct in-person clinical characterization. As a result, this study could not independently confirm the diagnostic status of participants and administer dedicated cognitive assessments. However, previous studies have demonstrated that parent-report of children's IQ strongly correlates with standardized clinical IQ testing (Shu et al., 2022). Future work should collect well-validated in-person cognitive assessments to more accurately characterize the sample and examine how NET measures relate to cognitive functioning. Longitudinal work with larger PHTS and other NDGS samples and longer follow-up will also be critical for evaluating age effects and changes in neurobehavioral processes across development, as well as sensitivity to intervention effects.

Given that a significant portion of individuals with NGDS have cognitive or language delays, we focused on the caregiver-report NET scales. Future work might benefit from including other informants and perhaps self-report versions of the NET measures especially for syndromes that include individuals with little to no cognitive deficits such as PHTS. Further, given the preliminary nature of this study, it was not possible to include a comprehensive set of additional instruments to establish convergent and divergent validity. Thus, additional validation work, including convergent and discriminant validity analyses, is needed to provide further support for the NET scales. Finally, although not a limitation per se, given that one of the guiding principles of the NET development was to deliver a neurobehavioral tool suitable for repeated administration without overburdening families, it is important to note that, due to this, domain coverage of the individual NET scales does not enable comprehensive clinical characterization. However, given that ESEM analyses indicated that most NET scales had multifactor structure, with excellent model fit and strong reliability, it is clear that NET scales provide at least adequate characterization of the crucial subdomains within neurobehavioral domains. As such, they may be useful for detailed phenotypic characterization in future research, as outcome measures in clinical trials, and, with sufficient norming, could facilitate clinical assessment.

5 | CONCLUSIONS

In summary, the present study provides preliminary evidence that the freely-available and online administered NET is a relatively brief, reliable assessment battery with preliminary evidence of factorial and concurrent validity and potential utility for the characterization of crucial neurobehavioral domains that are relevant for understanding individual differences in PHTS and other NGDS. Further, NET scales showed excellent measurement precision for capturing a wide range of abilities and showed strong test–retest replicability, which suggests good potential for its use for longitudinal research and intervention tracking. With further replication and the addition of online scoring and reporting, the NET has excellent potential for wide adoption across research and clinical contexts.

AUTHOR CONTRIBUTIONS

Thomas W Frazier, Mirko Uljarević, and Antonio Y Hardan designed the study. Thomas W Frazier and Mirko Uljarević collected the data. Thomas W Frazier and Mirko Uljarević had full access to the data and conducted the analyses. Thomas W Frazier, Mirko Uljarević, and Antonio Y Hardan drafted the initial manuscript. All authors critically reviewed and provided the feedback on the initial version of manuscript. All authors approved the final version of the manuscript.

ACKNOWLEDGMENTS

We are sincerely indebted to the generosity of the families and individuals who contributed their time and effort to this study. We would

also like to thank the PTEN Hamartoma Syndrome Foundation, the PTEN Research Foundation, the SYNGAP Research Fund, the Malan Syndrome Foundation, and the ADNP Kids Foundation for their support of this project.

Charis Eng is the Sondra J. and Stephen R. Hardis Endowed Chair of Cancer Genomic Medicine at the Cleveland Clinic and an ACS Clinical Research Professor. Mustafa Sahin is the Rosamund Stone Zander Chair at Boston Children's Hospital.

FUNDING INFORMATION

This study was funded by the PTEN Research Foundation (to Frazier and Uljarević), with additional support from the SYNGAP Research Fund, the Malan Syndrome Foundation, the ADNP Kids Foundation, Autism Speaks, and the Simons Foundation Autism Research Initiative. The content is solely the responsibility of the authors and does not necessarily represent the official views of any of the funding agencies.

CONFLICT OF INTEREST STATEMENT

Dr. Frazier has received funding or research support from, acted as a consultant to, received travel support from, and/or received a speaker's honorarium from the PTEN Research Foundation, SYNGAP Research Fund, Malan Syndrome Foundation, ADNP Kids Research Foundation, Quadrant Biosciences, Autism Speaks, Impel NeuroPharma, F. Hoffmann-La Roche AG Pharmaceuticals, the Cole Family Research Fund, Simons Foundation, Ingalls Foundation, Forest Laboratories, Ecoeos, IntegraGen, Kugona LLC, Shire Development, Bristol-Myers Squibb, Roche Pharma, National Institutes of Health, and the Brain and Behavior Research Foundation, is employed by and has equity options in Quadrant Biosciences/Autism Analytica, has equity options in MaraBio and Springtide, and has an investor stake in Autism EYES LLC and iSCAN-R. Dr. Kolevzon has received funding or research support from, or acted as a consultant to ADNP Kids Research Foundation, David Lynch Foundation, Klingestein Third Generation Foundation, Ovid Therapeutics, Ritrova Therapeutics, Acadia, Alkermes, Jaguar Therapeutics, GW Pharmaceuticals, Neuren Pharmaceuticals, Scioto Biosciences, and Biogen. Dr. Sahin reports grant support from Novartis, Biogen, Astellas, Aeovian, Bridgebio, and Aucta. He has served on Scientific Advisory Boards for Novartis, Roche, Regenxbio, SpringWorks Therapeutics, Jaguar Therapeutics and Alkermes. The authors have no other competing interests.

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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How to cite this article: Frazier, T. W., Busch, R. M., Klaas, P., Lachlan, K., Jeste, S., Kolevzon, A., Loth, E., Harris, J., Speer, L., Pepper, T., Anthony, K., Graglia, J. M., Delagrammatikas, C., Bedrosian-Sermone, S., Beekhuyzen, J., Smith-Hicks, C., Sahin, M., Eng, C., Hardan, A. Y., & Uljarević, M. (2023). Development of informant-report neurobehavioral survey scales for PTEN hamartoma tumor syndrome and related neurodevelopmental genetic syndromes. *American Journal of Medical Genetics Part A*, *191*A:1741–1757. https://doi.org/10.1002/ajmg.a.63195