Received: 14 February 2023 | Revised: 4 May 2023 | Accepted: 18 May 2023

DOI: 10.1002/ajmg.a.63312

REVIEW ARTICLE

AMERICAN JOURNAL OF medical genetics PART A WILEY

Updated consensus guidelines on the management of Phelan–McDermid syndrome

Siddharth Srivastava[1,2] | Mustafa Sahin[1,2] | Joseph D. Buxbaum[3,4,5,6] | Elizabeth Berry-Kravis[7,8,9] | Latha Valluripalli Soorya[10] | Audrey Thurm[11] | Jonathan A. Bernstein[12] | Afua Asante-Otoo[13] | William E. Bennett Jr[14] | Catalina Betancur[15] | Tegwyn H. Brickhouse[16] | Maria Rita Passos Bueno[17] | Maya Chopra[1,2] | Celanie K. Christensen[18,19] | Jennifer L. Cully[20] | Kira Dies[1,2] | Kate Friedman[3,4] | Brittany Gummere[21] | J. Lloyd Holder Jr[22] | Andres Jimenez-Gomez[23] | Carolyn A. Kerins[24] | Omar Khan[25] | Teresa Kohlenberg[26] | Ronald V. Lacro[27] | Lori A. Levi[28] | Tess Levy[3] | Diane Linnehan[29] | Loth Eva[30] | Baharak Moshiree[31] | Ann Neumeyer[32] | Scott M. Paul[13] | Katy Phelan[33] | Antonio Persico[34] | Robert Rapaport[35] | Curtis Rogers[36] | Jeffrey Saland[35] | Swathi Sethuram[37] | Janine Shapiro[38] | Phillip I. Tarr[39] | Kerry M. White[18,40] | Jordan Wickstrom[41] | Kent M. Williams[42] | Dana Winrow[43] | Brian Wishart[44] | Alexander Kolevzon[3,4,35]

Correspondence
Alexander Kolevzon, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1230, New York, NY 10029, USA.
Email: alexander.kolevzon@mssm.edu

Funding information
Eunice Kennedy Shriver National Institute of Child Health and Human Development; National Center for Advancing Translational Sciences; National Institute of Mental Health; National Institute of Neurological Disorders and Stroke, Grant/Award Number: K23NS119666; National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NINDS); National Center for Advancing Translational Sciences (NCATS)

Abstract

Phelan–McDermid syndrome (PMS) is a genetic condition caused by *SHANK3* haploinsufficiency and characterized by a wide range of neurodevelopmental and systemic manifestations. The first practice parameters for assessment and monitoring in individuals with PMS were published in 2014; recently, knowledge about PMS has grown significantly based on data from longitudinal phenotyping studies and large-scale genotype–phenotype investigations. The objective of these updated clinical management guidelines was to: (1) reflect the latest in knowledge in PMS and (2) provide guidance for clinicians, researchers, and the general community. A taskforce was established with clinical experts in PMS and representatives from the parent community. Experts joined subgroups based on their areas of specialty, including genetics, neurology, neurodevelopment, gastroenterology, primary care, physiatry, nephrology, endocrinology, cardiology, gynecology, and dentistry. Taskforce members convened regularly between 2021 and 2022 and produced specialty-specific guidelines based on iterative feedback and discussion. Taskforce leaders then established consensus within their respective specialty group and harmonized the guidelines. The

For affiliations refer to page 2038

knowledge gained over the past decade allows for improved guidelines to assess and monitor individuals with PMS. Since there is limited evidence specific to PMS, intervention mostly follows general guidelines for treating individuals with developmental disorders. Significant evidence has been amassed to guide the management of comorbid neuropsychiatric conditions in PMS, albeit mainly from caregiver report and the experience of clinical experts. These updated consensus guidelines on the management of PMS represent an advance for the field and will improve care in the community. Several areas for future research are also highlighted and will contribute to subsequent updates with more refined and specific recommendations as new knowledge accumulates.

KEYWORDS
assessment, autism spectrum disorder, monitoring, Phelan–McDermid syndrome, SHANK3, treatment

1 | INTRODUCTION

Phelan-McDermid syndrome (PMS) is a genetic condition caused by *SHANK3* haploinsufficiency due to a chromosomal 22q13.3 deletion encompassing *SHANK3* or a *SHANK3* sequence variant. SHANK3 is a postsynaptic density scaffolding protein located in excitatory synapses. SHANK3 has multiple roles, including interfacing with ion channel receptors, signaling molecules, and cytoskeletal proteins (Durand et al., 2007; Naisbitt et al., 1999), as well as regulating dendritic spine maturation (Sala et al., 2001). Individuals with PMS experience a wide range of neurodevelopmental and systemic manifestations, including global developmental delay/intellectual disability (ID), impaired/limited language, autism spectrum disorder (ASD), hypotonia, epilepsy, congenital heart defects, gastrointestinal (GI) disorders, and urogenital malformations (Phelan et al., 2001; Soorya et al., 2013).

Current guidelines for evaluating and monitoring PMS have existed since 2014 and established recommendations pertinent to multiple medical specialties. The main basis for these recommendations was 13 published case series describing close to 600 affected individuals (Kolevzon, Angarita, et al., 2014).

More recently, knowledge surrounding PMS has grown significantly, and there is now data from randomized controlled trials (Fastman et al., 2021; Kolevzon et al., 2022; Kolevzon, Bush, et al., 2014; Zwanenburg, Bocca, et al., 2016), large-scale genotype–phenotype investigations (Levy et al., 2022; Nevado et al., 2022; Sarasua et al., 2014), and neurobehavioral phenotyping studies (Gergoudis et al., 2020; Srivastava et al., 2021). The Developmental Synaptopathies Consortium (DSC) is a research collaboration of medical centers throughout the United States focused on three rare genetic causes of ASD and ID including PMS that launched in 2014. One of its projects is a multisite, prospective, longitudinal, observational cohort study evaluating the genotype, phenotype, and natural history of PMS (ClinicalTrial.gov identifier NCT02461420).

This additional knowledge has necessitated an update to clinical management guidelines for PMS. To accomplish this goal, we established a taskforce of PMS clinical experts and representatives from the parent community. Our primary objective was to generate updated recommendations for the clinical management of PMS which (1) reflect the latest in knowledge about the disorder and (2) provide guidance for clinicians, researchers, and the general community.

As part of this taskforce, experts joined one or more of the following subgroups based on their areas of specialty: genetics, neurology, neurodevelopment (including psychiatry, psychology, speech and language pathology), gastroenterology, primary care, physiatry, nephrology, endocrinology, cardiology, gynecology, and dentistry. The task force members represented more than 20 different academic institutions from the United States, Europe, and South America; encompassed diverse ethnic backgrounds; and included males/females. Importantly, a parent/caregiver from the PMS community also joined each sub-group to ensure adequate representation from the family perspective.

Members of each subgroup convened regularly between 2021 and 2022 and produced specialty-specific guidelines based on iterative feedback and discussion. The taskforce leaders then established consensus within their respective specialty group and harmonized the guidelines. Summaries of recommendations for each specialty are presented in Tables 1–12. Definitions for some genetic terms used in this article are listed in Table 13.

Regarding nomenclature, a recent proposal has suggested that individuals with PMS in the setting of *SHANK3* haploinsufficiency receive the label of "PMS-*SHANK3* related," in contrast to individuals with interstitial deletions of Chromosome 22 without involvement of *SHANK3*, or "PMS-*SHANK3* unrelated" (Phelan et al., 2022). The guidelines presented here are based on data about individuals who have deletions that include *SHANK3* or *SHANK3* sequence variants because in general, published literature and research efforts to date have defined PMS based on *SHANK3* haploinsufficiency (OMIM no. 606232). We have therefore focused our efforts on consolidating the evidence from the vast amount of studies which indicate that *SHANK3* is the critical gene in PMS (Bonaglia et al., 2001, 2006, 2011;

Durand et al., 2007) and that de novo sequence variants in *SHANK3* have been identified in cohorts ascertained for ASD and ID (Boccuto et al., 2013; De Rubeis et al., 2014; Durand et al., 2007; Fu et al., 2022; Gauthier et al., 2009; Gong et al., 2012; Hamdan et al., 2011; Leblond et al., 2014; Lelieveld et al., 2016; Moessner et al., 2007; O'Roak et al., 2014; Satterstrom et al., 2020; Yuen et al., 2017).

2 | RESULTS

2.1 | Genetics

2.1.1 | Diagnosis

Increasingly, individuals are diagnosed with PMS as part of a molecular genetic evaluation for global developmental delay/ID and/or ASD without prior suspicion of the syndrome. Clinical features that may increase suspicion of PMS include mild dysmorphic features (bulbous nose, periorbital fullness, long eyelashes, fleshy hands, and dysplastic toenails), absent speech, epilepsy, renal malformations, and lymphedema. Evidence of *SHANK3* haploinsufficiency may be identified by methods including chromosomal microarray (CMA) and next-generation sequencing (NGS). Most cases of PMS are due to 22q13 deletions, although *SHANK3* sequence variants are increasingly identified as NGS becomes more available. Rarely, haploinsufficiency can result from a balanced rearrangement with a breakpoint that disrupts *SHANK3*.

2.1.2 | Genotype–phenotype relationships

Haploinsufficiency of *SHANK3* causes ID, ASD, hypotonia, motor impairment, epilepsy, increased pain tolerance, and GI problems in PMS (De Rubeis et al., 2018). Some features observed in PMS due to 22q13.3 deletions may be unrelated to monoallelic loss of *SHANK3*. Renal/urinary tract abnormalities and lymphedema are reported in 24%–40% and 7%–23%, respectively, of individuals with 22q13.3 deletions (Levy et al., 2022; Samogy-Costa et al., 2019; Soorya et al., 2013). However, among individuals with *SHANK3* sequence variants and small deletions involving only *SHANK3*, renal anomalies are not reported (Levy et al., 2022; De Rubeis et al., 2018), and lymphedema is reported in only 1% of cases (Levy et al., 2022).

Genotype–phenotype studies have elucidated several relationships in PMS. A large genotype–phenotype analysis of 170 individuals with PMS stratified variants into three categories: Class I deletions (deletions which include *SHANK3* only or *SHANK3* with *ARSA* and/or *ACR* and *RABL2B*, with loss of a single copy of the latter three genes not expected to contribute to the phenotype); Class II deletions (all other deletions); and *SHANK3* sequence variants. Those with Class I deletions or sequence variants had milder language, cognitive, and motor deficits—but more frequent skill regressions—versus those with Class II deletions. In addition, the former group had a greater risk for psychiatric diagnoses, such as bipolar disorder, depression, and schizophrenia (Levy et al., 2022). Alternatively, a smaller study in a cohort of 22 individuals with PMS showed significant methylation differences compared with controls in those with deletions of at least 1 Mb, but not in the group with smaller deletions (Schenkel et al., 2021).

There is a correlation between larger deletion size and increased neurodevelopmental severity in PMS (Nevado et al., 2022; Sarasua et al., 2014; Soorya et al., 2013), further indicating that genes proximal to *SHANK3* contribute to phenotypic severity in individuals with larger deletions. *TCF20*, a gene in the deleted interval in some patients, is implicated in an autosomal dominant neurodevelopmental disorder, characterized by variable dysmorphic features, ID, ASD, hypotonia, movement disorders, sleep disturbances, seizures, and structural brain abnormalities (Torti et al., 2019). *TCF20* is located 8.7 Mb from the 22q telomere, thus contributing to the phenotype in only the largest 22q13 terminal deletions.

The presence of certain systemic abnormalities in PMS may be related to haploinsufficiency of genes other than *SHANK3*. *CELSR1* (affected by terminal 22q13 deletions larger than 4.3 Mb) is implicated in autosomal dominant lymphedema (Erickson et al., 2019; Gonzalez-Garay et al., 2016; Maltese et al., 2019). Accordingly, lymphedema in PMS is primarily observed in individuals with deletions >4.3 Mb (Levy et al., 2022; Samogy-Costa et al., 2019; Soorya et al., 2013).

2.1.3 | Recommendations (Table 1).

Diagnostic testing

Genetic evaluation for PMS should include evaluation for both 22q13 deletions and *SHANK3* sequence variants. Deletions may be detected by CMA and many NGS-based methods. Some deletions may be smaller than the limit of detection for specific CMA or NGS assays. Depending on the specific test used to detect a deletion, additional testing may be indicated to characterize its extent. *SHANK3* sequence variants (including single nucleotide variants and small insertions and deletions) are typically assessed by NGS-based methods such as gene panels, exome sequencing, and genome sequencing. Rarely, a balanced rearrangement can disrupt *SHANK3*. Balanced rearrangements affecting *SHANK3* may be detectable by karyotype or some NGS-based methods. We recommend genetic counseling prior to genetic testing and concurrently with return of results. Following the diagnosis of PMS, referral to a clinical geneticist or other specialists familiar with the interdisciplinary management of the condition is recommended.

Identification of a deletion. The finding of a deletion of 22q13 can indicate the presence of an unbalanced chromosomal rearrangement such as a translocation or inversion. For example, a terminal deletion in conjunction with duplication of the terminal segment of another chromosome is consistent with an unbalanced reciprocal chromosome translocation. All patients with a terminal deletion should undergo testing by karyotype and fluorescence in situ hybridization (FISH) to

TABLE 1 Recommendations pertaining to genetic considerations in Phelan–McDermid syndrome (PMS).

Cause of PMS	Recommendations
All causes of PMS	Involve genetic counseling prior to testing of the patient or family members and again with the return of results
	Diagnostic testing should include evaluation for 22q13 deletions and *SHANK3* sequence variants. This may include CMA and NGS-based methods
	Following diagnosis of PMS, refer to a clinical geneticist or other specialist familiar with the interdisciplinary management of the condition
SHANK3 sequence variant	Send parental testing following the identification of a *SHANK3* sequence variant
Any deletion	If the *ARSA* gene is deleted, consider screening for MLD with urine sulfatides
Terminal deletion	Send a karyotype and FISH studies for the patient following the identification of an apparent terminal deletion to assess for the presence of an unbalanced translocation or a ring chromosome
	Send parental karyotypes and FISH studies following the identification of a terminal deletion[a]
Interstitial deletion	Send parental karyotypes and FISH studies following identification of an interstitial deletion[a]
Ring chromosome 22	Send parental karyotypes to assess for a mosaic ring chromosome
	Screen for complications of NF2 as described in Sections 2.2 and 2.5

Note: For recurrence risk counseling, please see Figure 1.
Abbreviations: CMA, chromosomal microarray; FISH, fluorescence *in situ* hybridization; MLD, metachromatic leukodystrophy; NF2, neurofibromatosis type 2; NGS, next generation sequencing.
[a]When a deletion in a patient is smaller than can be detected by FISH, CMA or NGS-based methods can potentially be used for parental testing with the understanding that balanced rearrangements may not be detected.

assess for an unbalanced rearrangement. Following the identification of an unbalanced rearrangement in an individual with PMS, we recommend parental studies to assess its origin using FISH studies and/or karyotyping depending on the rearrangement identified in the patient.

The detection of a 22q13 terminal deletion may also indicate the presence of a ring chromosome 22, a circular structure formed when the distal long arm and the distal short arm of the chromosome truncate and join. Therefore, an additional rationale for karyotyping following the detection of a terminal deletion is to assess for the presence of a ring chromosome. Individuals with ring chromosome 22 are at increased risk of developing neurofibromatosis type 2 (NF2) due to mosaic aneuploidy of chromosome 22 followed by a somatic second hit in the *NF2* gene (located at 22q12.2) that results in biallelic loss of function. We recommend that individuals with ring chromosome 22 undergo monitoring for complications of NF2 (provided in Sections 2.2 and 2.5).

Loss of a ring chromosome 22 followed by a somatic second hit can also result in biallelic inactivation of another tumor suppressor gene, *SMARCB1* (located at 22q11.2). Complete somatic loss of *SMARCB1* can lead to formation of a central nervous system (CNS) atypical teratoid/rhabdoid tumor (ATRT; Byers et al., 2017). There are case reports of ATRT in individuals with ring chromosome 22 (Byers et al., 2017; Cho et al., 2014; Sathyamoorthi et al., 2009).

22q13 deletions can unmask autosomal recessive single-gene disorders if a pathogenic variant is present on the other allele. Examples include metachromatic leukodystrophy (MLD; *ARSA* defect) and megalencephalic leukoencephalopathy with subcortical cysts (MLC; *MLC1* defect). There are a few case reports of individuals with PMS and MLD who presented with progressive neurological deterioration (Ahn et al., 2020; Bisgaard et al., 2009; Mingbunjerdsuk et al., 2021). Because patients with presymptomatic or early-stage MLD may be candidates for hematopoietic stem cell transplantation, some authors suggest MLD screening with urine sulfatides at the time of diagnosis of PMS associated with a deletion including ARSA (Mingbunjerdsuk et al., 2021).

Identification of a SHANK3 *sequence variant.* The majority of pathogenic *SHANK3* sequence variants occur de novo. For individuals with a variant of uncertain significance (VUS; as defined in Richards et al., 2015), we recommend parental testing to determine inheritance status. The finding of a *SHANK3* VUS inherited from a healthy, neurotypical parent argues against the pathogenicity of the variant. For individuals with pathogenic or likely pathogenic *SHANK3* variants, we recommend parental testing to evaluate for the (rare) possibility of mosaicism or a mildly affected parent. While the likelihood of detecting mosaicism is low, if present, the risk of recurrence may increase up to 50%.

Recurrence risk counseling

We recommend genetic counseling for families in which PMS has been diagnosed. In this context, parental testing should be offered following the identification of a deletion including *SHANK3* or a pathogenic *SHANK3* variant. The recommended approach to parental testing and a summary of possible outcomes is shown in Figure 1. For interested families who are at increased risk of having future affected offspring, genetic counseling should include discussion of the option of prenatal testing and preimplantation genetic diagnosis.

Terminal deletions. For parents of individuals with terminal 22q13 deletions in isolation or in the context of a chromosomal rearrangement, we recommend karyotype and FISH testing to assess de novo status and the possibility of a predisposing rearrangement. Normal parental studies predict a low recurrence risk (empirically <1%, due to the possibility of gonadal mosaicism). In the rare case that a parent harbors a deletion, the recurrence risk in his/her offspring is predicted 50%. When parents carry a chromosomal rearrangement such as an

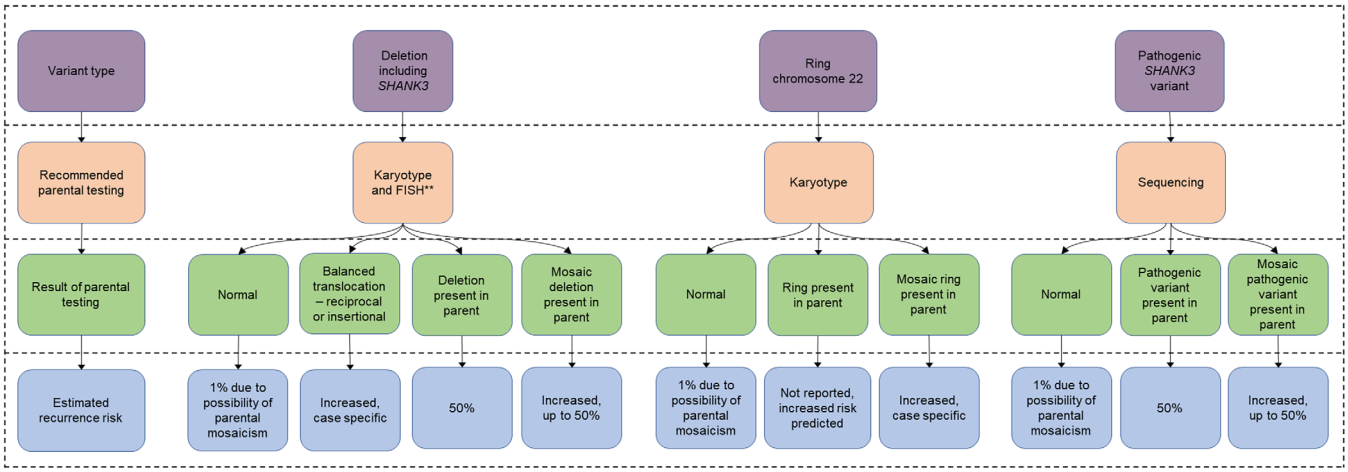

FIGURE 1 Recommendations for parental testing in Phelan–McDermid syndrome. We recommend parental testing following the identification of a 22q13 deletion including *SHANK3* or a pathogenic *SHANK3* sequence variant (orange). The estimated risk of familial recurrence (light blue) depends on the nature of the pathogenic variant (purple) in the proband and the results of parental testing (green). Karyotype and FISH can be used for parental evaluation of most deletions (see note below). Targeted sequencing may be used for parental evaluation of pathogenic *SHANK3* variants. FISH, fluorescence in situ hybridization. **When a deletion in a patient is smaller than can be detected by FISH, chromosomal microarray, or next generation sequencing-based methods can potentially be used for parental testing with the understanding that balanced rearrangements may not be detected.

unbalanced reciprocal translocation or inversion, there is an elevated, case dependent, recurrence risk. In ~50% of patients with complex chromosome rearrangements involving 22q13, a parent is a balanced rearrangement carrier (Phelan et al., 1993). There is also an increased recurrence risk if a parent is found to have mosaicism for a chromosome rearrangement such as a translocation, inversion, or ring chromosome.

Interstitial deletions. Most, but not all, interstitial deletions arise de novo. We recommend parental FISH and karyotype to evaluate for parental mosaicism or an insertional translocation. For interstitial deletions not detectable by FISH and karyotype, alternative methods can be utilized. If de novo status is confirmed, the recurrence risk is estimated to be low (empirically 1% or less, due to the possibility of gonadal mosaicism). There is an increased recurrence risk (case dependent) if a parent has an insertional translocation or exhibits somatic mosaicism. In the rare case that a parent has a nonmosaic deletion, the recurrence risk is 50%.

SHANK3 *sequence variants.* The majority of pathogenic variants in *SHANK3* are de novo. We recommend parental testing to confirm de novo status if trio sequencing did not occur initially. If parental testing is negative, there is a low empiric recurrence risk, commonly estimated <1% (attributable to the possibility of gonadal mosaicism). There are reports of four families with multiple affected siblings with *SHANK3* variants, consistent with gonadal mosaicism in one of the parents (Durand et al., 2007; Gauthier et al., 2010; Nemirovsky et al., 2015; Nevado et al., 2022). Detection of a pathogenic *SHANK3* variant in a mildly affected parent is possible due to variable expressivity (Tabet et al., 2017a). In this situation, the recurrence risk is 50%. Detection of a somatic mosaic pathogenic variant in a parent would confer a case-specific increased recurrence risk (Kankuri-Tammilehto et al., 2021).

Risk to children of affected individuals

To date, there are no reports in the literature of individuals with PMS having children. For an individual with PMS due to a 22q13 deletion or pathogenic *SHANK3* variant, the estimated risk of having an affected child with each pregnancy is 50%, consistent with autosomal dominant inheritance.

Risk to children of siblings of affected individuals

In most cases, the risk of an unaffected sibling of an individual with PMS having a child with PMS is low and similar to the general population risk. In families with parents who are balanced chromosome rearrangement carriers, we recommend offering karyotype and FISH to siblings who are family planning.

2.2 | Neurology

2.2.1 | Neuroimaging abnormalities

There is a spectrum of brain magnetic resonance imaging (MRI) abnormalities associated with PMS. These findings are largely nonspecific, including white matter changes (specifically T2 hyperintensities of the deep white matter), ventriculomegaly, arachnoid cysts, and cerebral/cerebellar atrophy (Holder & Quach, 2016; Srivastava et al., 2019). Most of these findings are nonactionable, except for hydrocephalus, which is a rare occurrence in PMS but may require ventricular shunting.

Neuroimaging may show additional abnormalities under specific circumstances. In the case of ring chromosome 22, MRI may show

NF2-specific findings, such as intracranial acoustic neuromas/vestibular schwannomas (Lyons-Warren et al., 2017; Ziats et al., 2020) as well as intraspinal meningiomas and ependymomas (Kresbach et al., 2021). In the rare co-occurrence of PMS and MLD, brain MRI may show changes consistent with the leukodystrophy, such as bilateral, symmetric, confluent periventricular white matter changes, as well as cortical and subcortical atrophy (Ahn et al., 2020). In MLC, brain MRI may show subcortical cysts and edema in the subcortical white matter (Bosch & Estévez, 2020).

Recommendations (Table 2).

The need for a baseline brain MRI after initial diagnosis of PMS depends on the cause of the syndrome. For an individual with PMS due to ring chromosome 22, we recommend brain and spine MRI

TABLE 2 Recommendations pertaining to neurological considerations in Phelan–McDermid syndrome.

Cause of PMS	Domain	Recommendations
Any cause of PMS	Neuroimaging abnormalities	Obtain brain magnetic resonance imaging (MRI; with gadolinium, unless there is an institutional policy in place about use of contrast agents) based on the following indications: 1. Focal neurological findings on exam 2. Focal seizures or focal abnormalities on electroencephalography (EEG) 3. Concerns for increased intracranial pressure 4. Regression (motor or dramatic language regression) 5. Macrocephaly 6. Microcephaly 7. Clinician judgment
		Perform repeat brain MRI based on the following reasons: 1. Sudden change in seizure frequency and/or characteristics 2. Changes in neurological examination 3. Regression 4. Clinician judgment
	Epilepsy and EEG abnormalities	Perform routine EEG for suspected seizures or epilepsy
		Prolonged EEG is warranted if: 1. Suspicion for seizures is high yet initial routine EEG is nondiagnostic 2. The EEG needs to capture sleep to establish a diagnosis like electrical status epilepticus of sleep
		Follow-up EEG is warranted in individuals who have: 1. Significant interictal epileptiform activity on previous EEGs if the results of follow-up EEG will change management 2. New symptoms suspicious for seizures 3. Unexplained developmental regression, especially in language or motor abilities 4. Unusual delay in expected developmental milestones compared with typical developmental progression seen with PMS
		Treatment and management of seizures in PMS are similar to standard practice
	Autoimmune encephalitis	Evaluate for autoimmune encephalitis in individuals who experience: 1. Abrupt regression 2. Onset of neuropsychiatric symptoms accompanied by new focal neurological signs including seizures 3. Onset of neuropsychiatric symptoms without accompanying focal neurological signs but which fail to respond to appropriate trials of psychotropic medications
		Work-up should include a lumbar puncture with standard cell count, protein level, and glucose level. Consider evaluation for autoimmune antibodies, including anti-NMDA receptor, anti-AMPA receptor, and anti-voltage gated potassium channel antibodies from both cerebrospinal fluid (CSF) and blood
		For those patients with positive autoantibodies from either CSF or serum, consider immune modulators, including intravenous methylprednisolone and intravenous immunoglobulin
		In cases associated with sudden onset of new neurologic symptoms (seizures, regression) where the work-up fails to identify any laboratory abnormalities, consider empirical use of immunomodulatory therapies, targeting presumed seronegative autoimmune encephalitis
Ring chromosome 22	Screening/surveillance	Obtain brain and spine MRI (with gadolinium) upon initial diagnosis
		Repeat brain MRI (with gadolinium) as part of surveillance schedule every 1–2 years after age 10 years until at least age 40 years
		Repeat spine MRI (with gadolinium) based on clinical symptoms
		Perform neurological examination upon initial diagnosis and then annually

Note: Recommendations pertaining to ring Chromosome 22 are in *addition* to those pertaining to any cause of PMS.

(with gadolinium), given the increased risk of NF2-related acoustic neuromas/vestibular schwannomas and spinal tumors. Without ring chromosome 22, reasons to consider baseline brain MRI (with gadolinium, unless there is an institutional policy in place about use of contrast agents) include focal neurological findings on exam; focal seizures or focal abnormalities on electroencephalogram (EEG); concerns for increased intracranial pressure; regression (motor regression or dramatic language regression); macrocephaly; microcephaly; and clinician judgment. In the absence of these factors, clinicians may consider brain MRI (without gadolinium) if there is a desire to establish a neuroimaging baseline in case neurological status changes in the future.

We recommend *repeating* brain MRI based on the following considerations: sudden change in seizure frequency and/or characteristics (especially new emergence of focal seizures); changes in neurological examination (including pyramidal or extrapyramidal findings); regression: clinician judgment. Repeating brain MRI as part of a surveillance schedule is not necessary in PMS, except in the presence of ring chromosome 22. For individuals with ring chromosome 22, we recommend repeating brain MRI with gadolinium every 1–2 years starting at age 10 years until at least age 40 years, in accordance with NF2-specific guidelines (Evans, 1993); it is not necessary to repeat spine MRI unless there are concerning symptoms.

2.2.2 | Epilepsy and EEG abnormalities

In individuals with PMS, epilepsy occurs with a varying prevalence ranging from 17% to 41%, and approximately half have a history of a single lifetime seizure (Holder & Quach, 2016; Jeffries et al., 2005; Khan et al., 2018; Soorya et al., 2013; Wilson et al., 2003). The onset of the first-lifetime seizure is likewise highly variable. Reported seizure semiologies include atypical absence, tonic, tonic–clonic, and myoclonic seizures. Electrographic seizures and status epilepticus are infrequently noted in PMS. Seizure burden and frequency are highly variable. The incidence and prevalence of intractable epilepsy in PMS are not well established (Holder & Quach, 2016; Khan et al., 2018). A small percentage of affected individuals can develop Lennox–Gastaut syndrome (Holder & Quach, 2016; Srikanth et al., 2021), an epilepsy syndrome characterized by multiple seizure types, refractory epilepsy, and characteristic EEG findings including slow spike-and-wave bursts. Among individuals with PMS who do not have epilepsy, epileptiform activity may still occur. EEG abnormalities include generalized slowing, multifocal slowing, focal spike and sharp waves, and generalized bursts of spike and slow-wave activity (Holder & Quach, 2016; Khan et al., 2018). Routine EEGs detect about 50% of the interictal epileptiform abnormalities seen in prolonged overnight EEG recordings containing portions of sleep (Khan et al., 2018; Table 2).

Recommendations (Table 2).

Electroencephalogram. The major limitation for recommendations regarding EEG in PMS is that most of the published data for EEG findings are based on single center, retrospective case series, and limited longitudinal patient databases. We recommend routine EEGs for all individuals with PMS who present with suspected seizures or epilepsy, regardless of age. Generally, EEGs should capture some sleep periods and have time-locked videos. We suggest a prolonged EEG (i.e., recording for multiple hours and preferably including overnight sleep data) in situations where (1) suspicion for seizures is high yet initial routine EEG is nondiagnostic, or (2) the EEG needs to capture sleep to establish a diagnosis like electrical status epilepticus of sleep. Additionally, we recommend follow-up EEG testing in individuals who have demonstrated one or more of the following: (1) significant interictal epileptiform activity on previous EEGs if the results of follow-up EEG will change management, (2) new symptoms suspicious for seizures, especially repetitive, stereotyped, and episodic symptoms with or without alteration of awareness or motor features (e.g., stereotyped nondistractible staring spells), (3) unexplained developmental regression, especially in language or motor abilities, and (4) unusual delay in expected developmental milestones compared with typical developmental progression seen with PMS.

EEG can be a difficult procedure to tolerate for some individuals with PMS due to issues such as anxiety about equipment and tactile defensiveness. However, behavioral training approaches may be helpful in desensitizing individuals to this procedure, increasing tolerability. These approaches may include mock EEG placement procedures, in conjunction with continuous positive reinforcement (music, stories, and other preferred activities; Slifer et al., 2008).

Epilepsy treatment. Treatment and management of seizures in PMS are similar to standard epilepsy practice. After two lifetime unprovoked seizures, or one lifetime unprovoked seizure with EEG suggesting a high likelihood for having future unprovoked seizures, we recommend starting an antiseizure medication. There are no antiseizure medications shown to be more beneficial than others in PMS. The first-choice medication should match the predominant seizure type (sodium channel inhibitors like oxcarbazepine for focal-onset seizures versus broad-spectrum medications like lamotrigine, divalproex, levetiracetam, or brivaracetam for generalized seizures). Levetiracetam has the benefit of ease of access, lack of need for routine monitoring, and fewer drug interactions, but anecdotal reports suggest behavioral side effects in some affected individuals despite concurrent use of pyridoxine. Epidiolex (containing a purified form of cannabidiol) is currently approved by the U.S. Food and Drug Administration (FDA) for use in individuals with Lennox–Gastaut syndrome or Dravet syndrome. However, there is no data yet on the use or efficacy of cannabidiol products for epilepsy in PMS.

We recommend stopping anti-seizure medications if the individual is seizure-free for at least 2 years, with some exceptions. We suggest considering longer duration of anti-seizure medication treatment if the individual has an underlying condition associated with significant seizure risk (such as a structural brain abnormality), if the seizures were previously very difficult to control, or if the most recent EEG shows substantial epileptiform activity. Therefore, after a 2-year seizure-free period, a repeat EEG is recommended.

If antiseizure medications are not effective at controlling seizures, alternative approaches are available although not specifically tested in PMS. The ketogenic diet provides good seizure control to some individuals with intractable seizures and is an option when multiple medications fail or when there are problems with medication side effects. The ketogenic diet works best for children under the age of 4 years and when the family and child are motivated to strictly follow the diet. The diet works best for atonic and absence seizures but can work for all seizure types. A vagal nerve stimulator is a small device implanted by surgery at the base of the neck on the vagal nerve, which it then stimulates. We suggest considering epilepsy surgery evaluation for individuals with very difficult to control focal seizures. Epilepsy surgery can sometimes be useful for epilepsy affecting the entire brain if the seizures are uncontrolled and there is one area from which most seizures arise.

2.2.3 | Evaluation for autoimmune encephalitis

A recent report described four adolescent girls with PMS who developed subacute neuropsychiatric symptoms associated with behavioral or developmental regression. Each treating physician independently considered autoimmune encephalitis as a potential etiology of the regressive episode. Diagnostic studies were generally unrevealing, with normal neuroimaging, normal cerebrospinal fluid (CSF) studies (one had nine white blood cells), and negative serum antibody titers including NMDA receptor antibody. Nevertheless, treatment with immunomodulation therapies including oral or intravenous steroids, intravenous immunoglobulins (IVIG), and other medications (rituximab, cyclophosphamide, and mycophenolate) resulted in symptomatic improvement (Bey et al., 2020). In PMS, the area of neuropsychiatric presentations sensitive to immune modulation requires further study. There is no data yet definitely stating whether individuals with PMS are at an increased risk for autoimmune encephalitis.

Recommendations (Table 2).

We recommend an evaluation for autoimmune encephalitis in individuals with PMS who experience (1) abrupt regression, (2) onset of neuropsychiatric symptoms accompanied by new focal neurological signs including seizures, or (3) onset of neuropsychiatric symptoms without accompanying focal neurological signs but which fail to respond to appropriate trials of psychotropic medications. The work-up should include a lumbar puncture with standard cell count, protein level, and glucose level. Furthermore, providers should consider evaluation for autoimmune antibodies, including anti-NMDA receptor, anti-AMPA receptor, and anti-voltage gated potassium channel antibodies from both CSF and blood.

For those patients with positive autoantibodies from either CSF or serum, we recommend immune modulators, including IV methylprednisolone and IVIG. In those who continue to have significant symptoms despite these immunomodulatory therapies, consider other immune modulators, such as rituximab and cyclophosphamide. In cases associated with sudden onset of new neurologic symptoms (such as seizures, regression) that have prompted an autoimmune encephalitis work-up but where the work-up fails to identify any laboratory abnormalities, consider empirical use of immunomodulatory therapies, targeting presumed seronegative autoimmune encephalitis.

2.3 | Neurodevelopment

2.3.1 | Intellectual disability

ID is a neurodevelopmental disorder characterized by impaired intellectual and adaptive functioning and is present in the vast majority of individuals with PMS, often in the severe-profound range (Droogmans et al., 2020; Ponson et al., 2018; Soorya et al., 2013; Zwanenburg, Ruiter, et al., 2016). However, some individuals may have mild/moderate ID or even normal IQ (Samogy-Costa et al., 2019; Tabet et al., 2017b). ID persists throughout the lifespan. Lower IQ with age is expected and not necessarily a sign of regression but rather may reflect the individual with PMS making slower cognitive progress than a typical child. Growth scores, also known as person-ability scores (or raw scores if growth scores are not available on the instrument used for assessment) are needed to distinguish true regression from the expected slower-than-normal growth rate. There may be a subgroup of individuals with PMS who show particular declines in cognitive measures around adolescence, due to lack of skills progression or loss of previously acquired skills (Kankuri-Tammilehto et al., 2021; Kohlenberg et al., 2020; Kolevzon et al., 2019; Reierson et al., 2017; Verhoeven et al., 2020).

Recommendations (Table 3).

Periodic monitoring and actual testing of cognitive skills over time (at least annually, if feasible) may help families and providers track changes. Floor effects on standardized tests are expected in those with severe/profound ID, so adaptations or out-of-range testing may be used. Growth scores should be monitored if possible to understand the rate of progress. We recommend concurrent assessment of difficulties in related domains, such as motor functioning and social communication, to help providers adjust interventions to individual profiles.

Early Intervention (EI) is important for optimizing early cognitive development in PMS, similar to other conditions affecting neurodevelopment. Physical therapy (PT) may be the first implemented EI service due to motor delays manifesting in infancy. In this context, we recommend assessing early play skills (e.g., imitation, matching, and puzzles) to evaluate early cognitive development. Empirically validated treatment models for enhancing cognitive skills include applied behavior analysis (ABA) therapy. Research suggests early intensive behavioral intervention is beneficial, according to one meta-analysis of early intensive interventions for children with ASD (Eldevik et al., 2009). There is data from a randomized, controlled trial evaluating the efficacy of the Early Start Denver Model (ESDM; a comprehensive intervention based on developmental and applied behavioral

TABLE 3 Recommendations for building independence in language, cognition, and daily living skills in Phelan–McDermid syndrome.

Domain	Educational interventions (recommendations for the school/ therapists)	Clinical interventions (recommendations for clinicians)	Enrichment activities (recommendations for the family)
Language (geared toward individuals considered minimally verbal)			
Receptive	Focus on teaching identification of common items that are part of simple directions and everyday routines	Refer to audiology (particularly important for those with ring chromosome 22)	Use simple phrases and exaggerated tone on key words
		Refer to speech and language therapy	Provide physical or model prompts following simple instructions to teach correct responses in an errorless manner
		Consider referrals to early intensive applied behavior analysis (ABA) therapy with a focus on Verbal Behavior and Pivotal Response Training	Practice identical matching of functional items
Expressive	Focus on teaching requests for highly preferred items and activities that can be easily and frequently delivered	Refer to speech and language therapy	Identify a few highly motivating items and activities; physically or verbally prompt the corresponding language depending on the individual's method of communication (e.g., sign, picture) and quickly deliver the item or activity
		Consider referrals to alternative augmentative communication (AAC) evaluation/training that prioritizes speaker ease and functional communication	Frequently practice requests for targeted items/activities
		Consider early referrals to intensive ABA with a focus on Verbal Behavior and Pivotal Response Training	
Speech	AAC may increase the likelihood of speech development and should be a consideration for most individuals	Refer to speech therapy	Provide rewards following sound productions to increase vocalization frequency
	Nonspeech oral motor exercises are NOT recommended for remediation of speech disorders	Consider early referrals to intensive ABA with a focus on Verbal Behavior	Encourage and highly reward any and all vocal imitation
			Practice general motor imitation activities (e.g., raising hands, clapping)
Cognition			
Early development	Early intervention should focus on cognitive development (e.g., targeting imitation, matching, and puzzles)		Consider parent-focused early intervention, including parent training, to help implement approaches throughout the day
General	Perform regularly scheduled curriculum-based assessments to monitor progress through an individual education plan	Consider periodic clinic-based cognitive (developmental) testing, especially if regression is observed; alternative tests may be needed (including out-of-age-range testing)	Encourage family activities which enhance generalization and maintenance of skills
	Assessments may need to include specialized tests for individuals with significant delays and/or physical and motor impairments	Help the family coordinate ABA and related behavioral approaches across environments (i.e., school and home)	Provide consistent communication to providers across environments about target goals and methods used (e.g., visual schedules)
	Consider ABA and other structured teaching approaches targeting		

(Continues)

TABLE 3 (Continued)

Domain	Educational interventions (recommendations for the school/therapists)	Clinical interventions (recommendations for clinicians)	Enrichment activities (recommendations for the family)
	preacademic, academic, and functional communication skills		
	Consider educational approaches used in special education, including small teacher-to-student ratios, full school year teaching, and individualized instruction		
Activities of daily living (ADLs)			
General	Work with the family to establish developmentally anchored, high-priority ADLs that consider additional disabilities and caregiving factors	Refer to physical, occupational, and speech and language therapy to teach and maintain skills in all areas that impact the individual's ability to perform ADLs	Increase opportunities to practice previously taught skills (i.e., programmed maintenance)
	ABA may help teach functional daily living skills, including visual schedules and task analyses	Help the family periodically set ADL goals, as informed by assessment as well as medical, cognitive, language skills, and/or history of regression	Consider social support, social services, and respite programming
			Coordinate with educational programs to facilitate ADL goals as well as maintenance and generalization of skills
Personal/Domestic	Strategies that promote personal care skills include (1) establishment of routines with visual and auditory prompts, (2) task analyses and chaining, (3) stimulus control procedures, and (4) hierarchical prompting	Use Vineland Adaptive Behavior Scales Personal and Domestic subdomain responses to promote discussion with family on priorities	Increase independent leisure activity options in home
		Carefully consider physical, medical, and environmental factors influencing toileting challenges	Reinforce imitation of, modeling of, and prompting for skills targeted in school
Community	Focus on goals that promote socialization and integration in community settings	Use Vineland Adaptive Behavior Scales Community subdomain responses to promote discussion with family on priorities for community skills	Identify supports needed to facilitate social/recreational activities for the affected individual and family
		Discuss with the family behavioral and medical challenges that may require support before the initiation of community goals	

analytic principles) versus community intervention in children 18–30 months of age with ASD. In contrast to the comparison group, children who received ESDM had larger improvements in measures of IQ and adaptive behavior. (Dawson et al., 2010). It should be noted that there is no evidence yet specifically indicating what types of developmental interventions are most effective for PMS.

Individuals with PMS often require sustained input to learn new skills in multiple domains. Structured teaching approaches may be used/adapted from other special education approaches (e.g., ASD specific). Examples include incorporating visuals to help children plan/execute/organize complex tasks (e.g., morning routine) and encouraging gesture use.

For school-age children, we recommend small student-to-teacher ratios, full school year teaching, and individualized instruction. Specific programs mentioned above may be used in conjunction with family-centered interventions (e.g., caregiver skills training) to enhance generalization and maintenance of taught skills.

2.3.2 | Communication impairment

Individuals with PMS typically present with absent or significantly disordered speech and language. Speech refers to the production of sounds, while language refers to vocabulary, syntax, and grammar

of words/signs. While most infants with PMS coo and babble to some extent (Brignell et al., 2021; Philippe et al., 2008), sound and syllable imitation may not occur, and meaningful words are unlikely to develop in accordance with typical speech-language developmental milestones. However, there can be variability, as some individuals develop the ability to engage in conversations. Individuals with sequence variants and smaller deletions typically have stronger expressive language (Brignell et al., 2021; Levy et al., 2022; Nevado et al., 2022; Sarasua et al., 2011, 2014).

In PMS, the language gap compared with the normative population widens with age. Receptive language skills may slightly exceed expressive language skills in people with PMS (though both are often at or below the 12-month level; Soorya et al., 2013; Zwanenburg, Ruiter, et al., 2016), with the caveat that overestimation of receptive language levels is possible in individuals with severe developmental disabilities (Brignell et al., 2021). Some individuals with PMS use scripted phrases with good syntax and grammar that sound socially appropriate which can lead to assumptions of more intact receptive language.

Recommendations (Table 3).

Therapeutic interventions in PMS should prioritize efficient and functional communication. We suggest directly testing receptive language skills rather than presuming abilities based upon expressive language skills or parent/caregiver reports on standardized measures (Brignell et al., 2021). Those who do not demonstrate vocal imitation with the accuracy to support intelligible speech should potentially undertake evaluation for augmentative and alternative communication (AAC). Use of AAC does not hinder the development of vocal language and in fact may promote it (Romski et al., 2010).

AAC approaches include American Sign Language, idiosyncratic sign language, picture exchange, and speech-generating devices. Evaluators should consider activity level, problem behaviors, vision/hearing status, cognitive level, matching/scanning skills, gross motor/fine motor skills, and imitation skills when determining the best communication method (McGreevy et al., 2014). Selection of an approach should prioritize communication ease rather than potential for greatest language expansion, until the individual reaches the limits of a successful communication system. When possible, it is important to modify communication aids to reduce response effort on the "speaker."

2.3.3 | Impaired activities of daily living

Activities of daily living (ADLs) encompass everyday tasks that are necessary for independence in serving basic human needs, such as personal hygiene, feeding, health, household chores, leisure activities, and time/money management. Independence in ADL skills is inherently linked to development in other critical domains, such as communication, socialization, and cognition.

In PMS, complete independence in ADLs is rare, with most data suggesting individuals with PMS demonstrate ADL skills commensurate with cognitive levels (De Rubeis et al., 2018; Droogmans et al., 2020). Many older children and adults with PMS have ADL skills that fall within the 12–24 months old range of development (Phelan et al., 2001; Wilson et al., 2003; Zwanenburg, Ruiter, et al., 2016), though there can be considerable heterogeneity.

Recommendations (Table 3).

Given the interconnectedness of ADLs with other areas of development, we recommend that individuals with PMS receive routine monitoring, at least annually if feasible, of adaptive skills, with a focus on increasing independence. Treatment planning should focus on developing routines around ADLs (e.g., visual schedules), teaching new skills, and teaching compensatory strategies.

We recommend that ADL interventions occur on a daily basis and should balance teaching new skills with maintaining previously taught skills. It is necessary for educational and therapeutic programs to provide programming for generalization and maintenance of life skills and social-communication skills. It is important to ensure consistency of skills training and implementation across environments.

2.3.4 | Sleep disturbances

Sleep disturbances are common in PMS with a prevalence that ranges from 24% to 75% (Burdeus-Olavarrieta et al., 2021; Nevado et al., 2022; Philippe et al., 2008; Sarasua et al., 2014; Soorya et al., 2013), including 58%–85% of individuals with *SHANK3* sequence variants (De Rubeis et al., 2018; Moffitt et al., 2022; Nevado et al., 2022). Sleep disturbances encompass difficulty falling asleep, frequent night awakenings, and reduced total sleep time, similar to observations in many children with ASD (Hodge et al., 2014; Verhoeff et al., 2018). Onset of sleep disturbances may occur as early as at 4–5 months of life (Philippe et al., 2008). However, they are more frequently recognized by 5 years of age (Ingiosi et al., 2019) and particularly pronounced after 11 years of age (Smith-Hicks et al., 2021). One-third of adults with PMS suffer from sleep disturbances (Verhoeven et al., 2020), and one study using the PMS International Registry found that 54 of 60 cases (90%) of individuals 18 years and older continued to experience sleep disturbance (Moffitt et al., 2022). In PMS, sleep disorders include parasomnias, sleep apnea, restless leg syndrome, and periodic limb movement disorder (Bro et al., 2017). While some patients with PMS have undergone clinical nocturnal polysomnogram, the literature on sleep disturbance in PMS largely relies on caregiver report.

Sleep disturbances may appear as part of an incipient mood disorder. Nighttime insomnia and daytime sleepiness may precede the onset of mood/behavioral symptoms. In these cases, effective treatment of the underlying mood disorder may be essential to addressing the sleep disturbance.

Recommendations (Table 4).

Sleep hygiene techniques are the mainstay of improving sleep. Such techniques may include ensuring consistent bedtime routines; reducing

TABLE 4 Recommendations for behavior and sleep challenges in Phelan–McDermid syndrome.

Domain	Behavioral interventions	Pharmacological interventions
Challenging behavior and neuropsychiatric symptoms	Build "replacement" skills	Attention deficit, hyperactivity, and impulsivity: alpha-agonists; methylphenidate products; atomoxetine
	Consider Functional Behavioral Assessment (FBA) and Functional Communication Training (FCT) to manage challenging behaviors or changes in behavior associated with environmental, medical, and/or psychiatric issues	Aggression: alpha-agonists; *low-dose* second-generation antipsychotics (e.g., aripiprazole, risperidone, quetiapine, olanzapine); mood stabilizers (e.g., divalproex sodium, lamotrigine, lithium); or benzodiazepines
	Provide predictable routines with opportunities for making choices	Anxiety: selective serotonin reuptake inhibitors (with extreme caution), *N*-acetylcysteine, propranolol, trazodone, buspirone, mirtazapine, gabapentin, clomipramine, or benzodiazepines as needed
	Monitor mood, attention, and challenging behaviors	Mood cycling: mood stabilizers (e.g., divalproex sodium, lamotrigine, lithium); second-generation antipsychotics (e.g., aripiprazole, risperidone, quetiapine, olanzapine) if urgent help needed or severe symptoms present; combination strategies; and benzodiazepine augmentation
		Catatonia: lorazepam, electroconvulsive therapy, and mood stabilizers (divalproex sodium, lamotrigine, lithium)
Sleep	Organize the daily agenda so that exciting, motor, and cognitive activities occur in the afternoon up to dinner time and more relaxing activities occur between dinner and bedtime	Sleep onset difficulties: melatonin
	Avoid computer games and smartphone/tablet use, as well as demanding tasks, before bedtime	Difficulty staying asleep or early morning wakening: 5-Hydroxytryptophan or extended-release melatonin
	Define a bedtime routine, including a series of activities that represent a predictable and consistent "path to sleep" (e.g., put on pajamas, brush teeth, play a quiet game, get into bed, read a story with caregiver, turn off the light, and go to sleep)	Other options include clonidine, trazodone, doxepin, mirtazapine, quetiapine, gabapentin, benzodiazepines, zolpidem, amitriptyline, and antihistamines
	For adolescents and young adults, turn off, unplug, or remove smartphone and other electronic devices present in the bedroom	
	Make the bedroom a pleasant location associated with sleep and not with other exciting, stressful, or demanding activities	
	Reduce ambient light and noise to the extent possible	

stimulating activities before sleep; and reducing ambient light and noise in the bedroom. Commonly prescribed medication treatments for sleep disturbances include melatonin (for sleep onset disturbance; though there may be variability in actual content depending on manufacturer; Erland & Saxena, 2017), 5-hydroxytryptophan (to promote sleep maintenance), alpha agonists, antidepressants (e.g., trazodone, mirtazapine, doxepin), second-generation antipsychotics (e.g., quetiapine), gabapentin, benzodiazepines, or antihistamines, either alone or in combination (Bro et al., 2017; Kohlenberg et al., 2020). In the presence of restless legs, consider checking ferritin levels and adding iron supplementation if ferritin is <50 μg/L. Of note, guidelines exist for treatment of insomnia and disrupted sleep behavior in individuals with ASD which may be applicable here (Williams Buckley et al., 2020). For individuals where a sleep-related breathing disorder is suspected, night-time polysomnography should be considered.

2.3.5 | Challenging behavior and neuropsychiatric symptoms

Repetitive behavior and restricted interests (e.g., repetitive play, stereotyped language, and inflexibility with routines) are present in people with PMS, although generally less common than in people with ASD. Self-injurious behaviors in PMS include head-banging, skin-picking, and biting. Sensory reactivity symptoms are common and most frequently characterized by hyposensitivity across sensory domains (Droogmans et al., 2020; Serrada-Tejeda et al., 2022; Tavassoli et al., 2021; Mieses et al., 2016). An increased pain threshold is prevalent in PMS and can be associated with reduced response to potentially dangerous injuries (De Rubeis et al., 2018).

Symptoms associated with attention-deficit/hyperactivity disorder (ADHD), including impulsivity, are common in PMS, although it

may be difficult to make the diagnosis in the context of severe-profound ID.

The exact prevalence of ADHD in PMS is not clear, but one study showed that 16/32 (50%) cases had hyperactivity (Soorya et al., 2013). Aggression may occur as a behavioral outcome of underlying discomfort or anxiety or as an incipient manic switch in bipolar disorder.

Individuals with PMS may exhibit anxiety manifesting as disruptive or repetitive behaviors when stressed by performance-related demands, novel situations, or transitions. However, anxiety may be difficult to assess due to cognitive and language deficits.

There are increasing reports of PMS-associated mood changes, like irritability, depression, and mood cycling (Egger et al., 2016; Kohlenberg et al., 2020; Kolevzon et al., 2019; Verhoeven et al., 2020). Bipolar disorder appears to be more common among individuals with small deletions and *SHANK3* sequence variants (16%) compared with individuals with larger deletions (3%) (Levy et al., 2022). Typical symptoms include rapid fluctuations in mood and activity level, periods of intense agitation and aggression, and pronounced sleep and appetite disturbances. Psychosis is difficult to assess in nonverbal individuals, but new bizarre behavior and apparent response to auditory or visual hallucinations may occur in the context of mood disturbance (Kohlenberg et al., 2020; Messias et al., 2013; Verhoeven et al., 2020). The prevalence of diagnosed schizophrenia or schizoaffective disorder in PMS is ~5% (Levy et al., 2022).

Catatonia is a presentation of unusual motor, autonomic, and behavioral symptoms, often accompanied by profound alterations in alertness, emotional state, and communication. There is increased risk of catatonia among individuals with small deletions or *SHANK3* sequence variants compared with those with larger deletions (Kohlenberg et al., 2020; Kolevzon et al., 2019; Levy et al., 2022; Verhoeven et al., 2020). Catatonic periods may involve dramatically reduced motion and interaction (stuporous catatonia) or manifest as continuous movement with repeated and apparently meaningless behaviors that can include self-injury or aggression without obvious function (excited catatonia, or delirious mania). Treatment with antipsychotic medication may trigger or exacerbate catatonia in PMS. Individuals may shift between stuporous catatonia and excited catatonia. Malignant catatonia, accompanied by autonomic instability, can be rapidly life threatening; the presence of muscle rigidity, fever, and fluctuating vital signs require immediate assessment and treatment (Dhossche & Wachtel, 2010). The diagnosis of catatonia may be overlooked due to the overlap of some catatonia symptoms with common features of ASD and ID, such as motor stereotypies and negativism. It is critical to keep catatonia in mind when caregivers report deteriorating function, given implications for treatment.

The onset of neuropsychiatric difficulties may begin with dramatic worsening of anxiety and compulsive behaviors, and/or episodes of mania and depression. A small number of patients, mostly male, present with severe impulsive aggression, sometimes in the context of catatonia. In young women, onset of mania may be coincident with menstrual cycles (Kohlenberg et al., 2020). In the context of mania, new sleep difficulties can include complete insomnia lasting days, and mood episodes may be accompanied by the emergence of disorganized behavior and apparent psychosis.

Recommendations (Table 4).

Behavioral interventions are the first-line treatment of aggression, repetitive behavior, and self-injurious behaviors in PMS. An intensive behavioral program based on the principles of ABA may be necessary, irrespective of an ASD diagnosis. Because of severity of associated ID, individuals with PMS require intensive intervention and constant repetition of skills to make and consolidate gains.

Epilepsy as well as infectious, GI, dental, and metabolic problems can manifest in a wide range of behaviors that may appear neuropsychiatric in origin. Thorough investigation for and treatment of these conditions is essential. Because of reduced responsiveness to sensory stimuli such as pain, assessment for physical injury is crucial.

In terms of medication management, alpha-2 adrenergic receptor agonists are typically recommended as first-line treatment for ADHD symptoms in PMS. Stimulants such as methylphenidate products may be effective but are often poorly tolerated and can lead to an exacerbation of anxiety and irritability. Atomoxetine and viloxazine may help ADHD symptoms in PMS.

For anxiety and restricted and repetitive behaviors, clinicians often attempt to treat with selective serotonin reuptake inhibitors (SSRIs). However, individuals with PMS have a high incidence of side effects with SSRIs, including precipitated mania or worsening agitation (Kohlenberg et al., 2020). For this reason, we suggest either avoiding SSRIs in PMS or using them cautiously (starting at very low doses, using them for short periods of time, and conducting vigilant monitoring for worsening agitation or sleeplessness). While anxiety disorders are frequent in PMS, treating them is challenging, and there are no established, or especially reliable, medications for this indication. Anecdotal reports suggest benefit with buspirone, *N*-acetylcysteine, or gabapentin in some cases. Benzodiazepines are generally avoided for chronic anxiety but can be used on an as needed basis (i.e., PRN) for anxiety in PMS.

Mood cycling, irritability, and aggression are likely best treated with mood stabilizers such as divalproex sodium, lithium, or lamotrigine (Egger et al., 2017; Kolevzon et al., 2019; Serret et al., 2015; Verhoeven et al., 2020). Second-generation antipsychotic medications may help acute stabilization in these cases, but doses should be very low (Pasini et al., 2010), given risk of precipitating catatonia and high rates of side effects in general. Nevertheless, some individuals with PMS and mood cycling, irritability, and/or aggression tolerate and respond well to antipsychotics.

Catatonia responds well to established treatment protocols using lorazepam, often at high doses, and/or electroconvulsive therapy.

The PMS Neuropsychiatric Consultation Group (https://pmsf.org/neuropsychiatric-consultation-group/) is a valuable resource available to all physicians to consult on their challenging cases. This group has also developed detailed treatment recommendations available online (https://pmsf.org/wp-content/uploads/2022/12/Combined-PMS-NCG-Pharma-currentversion.pdf).

2.3.6 | Regression

If regression occurs in PMS, affected areas include cognitive functioning, daily living skills, communication skills, and other adaptive skills (Kohlenberg et al., 2020). Regression may also affect academics (reading, writing) and technology utilization (e.g., tablets; Kohlenberg et al., 2020). The pathophysiology of regression in PMS is not yet known.

Anecdotal and published accounts indicate regression in PMS may affect speech and/or language skills (Brignell et al., 2021; Kohlenberg et al., 2020). Characteristics of speech and language regression range from a notable reduction to complete absence of intelligibility and word production. Language regression in individuals with PMS typically happens around age 3 years but may also occur later (Reierson et al., 2017). In PMS, regression in language often occurs earlier than regression in other domains, such as motor functioning and self-help skills.

Loss of ADLs can occur in regression in PMS. In one study focusing on developmental regression, 53% of the sample (ages 4–48 years old) reported a regression and loss of self-help skills, often during the school-aged period (ages 6–12 years). The average age of regression was 6 years, and most of the skills lost during the regression were not regained (Reierson et al., 2017). In another study examining regression associated with neuropsychiatric changes, psychiatric decompensation had a median age of onset of 20 years, with ~55% of individuals reporting loss of skills, including those related to ADLs such as toileting (Kolevzon et al., 2019). Most of the time, ADLs are never *fully* recovered, although individuals can regain some of their skills (Kohlenberg et al., 2020).

Loss of skills can occur in the years after the onset of psychiatric illness in teens and young adults (Kohlenberg et al., 2020; Kolevzon et al., 2019). In about half of those with regression, lost skills return when the underlying neuropsychiatric illness is controlled, particularly if significant rehabilitation services are available (Kohlenberg et al., 2020).

Recommendations.

At present, there are no clear methods to prevent or treat regression but vigilant monitoring and aggressive intervention for potential triggers are necessary. EEG should be considered to rule out seizures, and brain imaging may identify structural abnormalities that could provide clues about the cause of the regression. Regression may also be the first indication of a second genetic disorder, including MLD, where brain MRI might be informative. If skills are lost, re-training is warranted, and the specific intervention will depend on the domain/s affected.

2.4 | Gastroenterology

2.4.1 | Gastroesophageal reflux, constipation/diarrhea, encopresis

PMS is characterized by a high prevalence of GI symptoms, including gastroesophageal reflux (GER), constipation/diarrhea, feeding problems, and pica (Kolevzon, Angarita, et al., 2014). Many case series have described GI symptoms in PMS and their effect on quality of life, but descriptions of GI symptom severity, range, and prevalence vary widely across studies, and a systematic assessment with standardized clinical criteria (e.g., Rome IV criteria) or gold-standard diagnostic testing (e.g., GI imaging, pH probe, motility studies) is lacking. Moreover, for some GI disorders, application of standardized clinical criteria relying on the ability to verbalize symptoms may be inadequate in PMS. Caveats aside, rates of constipation and diarrhea in affected individuals range from 19% to 84% (Hussong et al., 2020; Kohlenberg et al., 2020; Witmer et al., 2019; Xu et al., 2020). Rates of GER range from 42% to 59% (Sarasua et al., 2014; Soorya et al., 2013; Witmer et al., 2019). In a small cohort of 17 children with PMS studied at the National Institutes of Health (NIH), 4/17 had functional constipation, 13/17 had fecal incontinence, and 10/17 had GER, as assessed by Rome IV criteria (Witmer et al., 2019). Additionally, 13 cases had colonic transit studies using Sitz markers, which was abnormal in 2 of the 13 studies completed.

Encopresis, often with concomitant enuresis, occurs commonly in PMS, although it remains unclear what portion of affected patients have retentive fecal incontinence (constipation subtype) versus nonretentive fecal incontinence, a distinction not easily captured by questionnaires alone. In a cohort of 41 German individuals with PMS assessed with a standardized questionnaire, 79% reported fecal incontinence, but the bowel habit associations of this symptom were not determinable (Hussong et al., 2020).

In some cases, worsening GI symptoms may be associated with developmental regression or neuropsychiatric decompensation. In one cohort of patients with severe psychiatric disorders and regression, 32/38 (84%) had chronic constipation, compared with 15% of patients in the PMS International Registry (Kohlenberg et al., 2020). In the context of regression, families may describe toileting as a "lost" skill, but this aspect of regression requires additional study (Reierson et al., 2017).

Recommendations (Table 5).

Many individuals with PMS have a decreased response to painful stimuli, impairing the ability to fully delineate pain sources, including ones that are GI-related. Thus, when symptoms like sleep disturbance, behavioral changes, slow growth, or feeding problems are unexplained, we recommend a thorough GI evaluation.

Supportive strategies that are effective in individuals without PMS may also be helpful in PMS. Examples include sufficient soluble fiber intake, regular physical activity, and pelvic floor PT, although none of these therapies have been formally studied in PMS. Anecdotal data from families and clinicians favor the use of behavioral strategies like ABA therapy to improve toilet training and limit stool holding.

In the setting of GER, constipation, encopresis, functional vomiting disorders, and other GI disorders, we recommend early consideration of gastroenterology referral. Affected individuals may have GI manifestations of their symptoms that are atypical compared with those of patients usually referred to gastroenterology specialists. A referral to a neurogastroenterologist/motility specialist or

TABLE 5 Recommendations pertaining to gastroenterology considerations in Phelan–McDermid syndrome.

Domain	Recommendations
Gastroesophageal reflux, constipation/diarrhea, and encopresis	Consider a thorough gastrointestinal (GI) evaluation for the following unexplained symptoms: 1. Sleep disturbance 2. Behavioral changes 3. Slow growth 4. Feeding problems Supportive GI strategies that are effective in individuals without PMS may also be helpful in those with PMS, including: 1. Sufficient soluble fiber intake 2. Regular physical activity as feasible 3. Pelvic floor physical therapy Consider an early gastroenterology referral for the following indications: 1. Gastroesophageal reflux 2. Constipation 3. Encopresis 4. Functional vomiting disorders When standard therapies are not effective, consider referral to neurogastroenterologist (motility specialist), or gastroenterologist specializing in neurodevelopmental/ neuromuscular disorders
Rumination syndrome	Consider nonspecific strategies, such as introducing nonpalatable substances via gastronomy tube Consider behavioral approaches if appropriate in light of cognitive limitations Consider further diagnostic testing, such as antroduodenal manometry, in more complex cases
Liver disease	Elevated transaminase levels may indicate: 1. Autoimmune hepatitis 2. Nonalcoholic fatty liver disease 3. Drug-induced liver injury
Nutritional deficiencies	Individuals with functional gastric bypass (gastrectomy, gastrojejunostomy, or jejunostomy) should undergo laboratory monitoring for: 1. Copper deficiency 2. B_{12} deficiency 3. Neutropenia

gastroenterologist who specializes in children with neurodevelopmental/neuromuscular disorders may be helpful, especially when standard therapies have not been effective, although these experts may not always be available.

2.4.2 | Rumination syndrome

Rumination syndrome, a effortless regurgitation of ingested food, anecdotally occurs more frequently in PMS compared with the general population.

Recommendations (Table 5).

Nonspecific strategies to improve rumination, such as introduction of nonpalatable substances via a gastrostomy tube, have been successful in limited cases (Severio et al., 2015). Behavioral approaches to rumination syndrome are more challenging in PMS, given their requirement of certain cognitive abilities. Rumination syndrome is often difficult to diagnose, and many individuals with PMS have other foregut disorders such as GER, gastroparesis, and small bowel dysmotility. Further diagnostic testing, such as antroduodenal manometry, may be helpful in more complex cases.

2.4.3 | Liver disease

Autoimmune hepatitis (AIH) is a rare complication of PMS, with only two reported cases (Bartsch et al., 2010; Tufano et al., 2009). A query of the Phelan-McDermid Syndrome Data Network (PMS-DN) in 2021 found that 0/389 cases answered "yes" to having "Autoimmune Liver Failure" (unpublished data). The prevalence of AIH is about 1/10,000 in the general population (Francque et al., 2012). Given the rarity of PMS, even two instances of AIH may represent increased risk. However, given the rarity of these diagnoses, routine monitoring of transaminases is not likely to be helpful.

Liver dysfunction in PMS can sometimes be due to nonalcoholic fatty liver disease, which is characterized by hepatic steatosis not secondary to known causes like alcohol consumption, medication use, or genetic liver disease. There is report of a 20-year-old male with a 22q13.33 deletion including *SHANK3*, ID, epilepsy, and digestive problems who developed transaminitis, with liver ultrasound showing findings consistent with moderate steatosis (Boccuto et al., 2018).

Recommendations (Table 5).

In individuals with PMS and elevated transaminase levels, consider AIH and nonalcoholic fatty liver disease as possible causes. Other diagnostic possibilities include drug-induced liver injury, given the high degree of polypharmacy in patients with neurodevelopmental disorders.

GI manifestations of NF2

Individuals with ring chromosome 22 can rarely develop GI manifestations of NF2, such as GI nerve sheath tumors (Lasota et al., 2003). Individuals with NF2 do not have a higher risk of developing GI neurofibromatosis or GI stromal tumors characteristic of NF1. No specific endoscopic monitoring is recommended for screening for such tumors in NF2.

Pica

Pica and mouthing of nonfood items occur in >50% of individuals with PMS (De Rubeis et al., 2018). In the aforementioned NIH cohort, 2/17

individuals underwent esophagogastroduodenoscopy for removal of pica-related foreign body (Witmer et al., 2019).

2.4.4 | Nutritional deficiencies

PMS can predispose affected individuals to certain nutritional deficiencies. Some may develop zinc deficiency, possibly related to the association of SHANK3 with zinc uptake proteins in the CNS and GI tract (Pfaender et al., 2017). Feeding via gastrojejunostomy tube may raise the risk of copper and B_{12} deficiency, due to bypass of the stomach. This effect may be exacerbated by zinc supplementation, so those with zinc deficiency should also receive additional copper supplementation (Duncan et al., 2015). Copper deficiency itself can cause neutropenia.

Recommendations (Table 5).

Individuals with PMS and functional gastric bypass (gastrectomy, gastrojejunostomy, or jejunostomy) should undergo periodic laboratory monitoring for copper deficiency, B_{12} deficiency, and neutropenia. In addition to nutritional supplementation, behavioral strategies (e.g., ABA) are also recommended for treating pica.

2.5 | Primary care

2.5.1 | Spectrum of primary care issues

Children and adults with PMS can have multiple physical health issues commonly encountered in primary care. In this section, we will focus on vision, hearing, thermoregulation, immune system, and skin-related issues. Between 6% and 29% of individuals with PMS have strabismus (Xu et al., 2020; Sarasua et al., 2014; Soorya et al., 2013), and 3%–57% have ptosis (Phelan et al., 2001; Sarasua et al., 2014; Soorya et al., 2013). The incidence of hearing loss is ~3% (Samogy-Costa et al., 2019; Xu et al., 2020). Conductive hearing loss caused by eustachian tube dysfunction may be amenable to myringotomy tube placement. In the presence of NF2 manifestations due to ring chromosome 22, vestibular schwannomas may lead to sensorineural hearing loss (Ardern-Holmes et al., 2017). Thermoregulatory differences include overheating or turning red easily (De Rubeis et al., 2018; Sarasua et al., 2014; Xu et al., 2020) and decreased perspiration (De Rubeis et al., 2018; Sarasua et al., 2014; Xu et al., 2020). Recurrent infections, including upper respiratory infections (URIs) and ear infections, occur at rates of up to 60% in PMS (De Rubeis et al., 2018; Dhar et al., 2010; Samogy-Costa et al., 2019; Soorya et al., 2018; Xu et al., 2020). URIs and ear infections may be related to difficulty with sputum clearance and hypotonia (Phelan et al., 2001). In patients with recurring infections, immunodeficiency may be contributory, as it affects up to 12% of patients with PMS (Sarasua et al., 2014; Soorya et al., 2013; Xu et al., 2020). The incidence of cellulitis is 7%, based on one study (Sarasua et al., 2014). Atopic disease includes food allergies, asthma, and eczema (De Rubeis et al., 2018; Xu et al., 2020). Café au lait macules and skin tumors may be present in the setting of ring chromosome 22 leading to symptoms of NF2 (Ardern-Holmes et al., 2017). The prevalence of lymphedema increases with age and predominantly affects teenagers and adults (Dhar et al., 2010; Nesslinger et al., 1994; Samogy-Costa et al., 2019; Sarasua et al., 2014; Soorya et al., 2013; Xu et al., 2020).

Recommendations (Table 6).

For these medical concerns, we recommend standard management. To evaluate for refractive errors and strabismus, we recommend ophthalmology evaluation at the time of diagnosis and then yearly (which is also recommended for individuals with ring chromosome 22). To screen for hearing loss, we recommended audiology evaluation at the time of diagnosis and annually in the case of ring chromosome 22. We recommend avoiding extreme temperatures, providing adequate hydration, and using equipment such as fans and cold packs in hot environments. Thermoregulatory differences, which predispose to skin redness, can sometimes mask cellulitis. Having high clinical suspicion for cellulitis and starting timely treatment is important. We

TABLE 6 Recommendations pertaining to primary care considerations in Phelan–McDermid syndrome.

Cause of PMS	Domain	Recommendations
Any cause of PMS	Screening/ surveillance	Refer to ophthalmology at the time of diagnosis for yearly evaluations
		Refer to audiology at the time of diagnosis
	Heat sensitivity	Counsel on protective measures against overheating: avoid extreme temperatures; provide adequate hydration; use fans and cold packs in hot environments
	Skin infection	Counsel of protective measures against skin infection: appropriately clean skin breakdown; moisturize-affected areas; use protective clothing
	Lymphedema	Counsel on strategies for addressing lymphedema: exercise; maintain healthy body mass index; use custom fitted compression garments to reduce extremity volume and slow disease progression
Ring chromosome 22	Screening/ surveillance	Refer to ophthalmology at the time of diagnosis for yearly evaluations
		Refer to audiology at the time of diagnosis for yearly evaluations
		Refer to dermatology at the time of diagnosis for yearly evaluations

Note: Recommendations pertaining to ring chromosome 22 are in *addition* to those pertaining to any cause of PMS.

recommend skin infection prevention measures, including appropriately cleaning skin breakdown, moisturizing the affected area, and using protective clothing. In those with ring chromosome 22, we recommend annual evaluation by a clinician experienced in neurofibromatosis to screen for skin tumors and other stigmata of NF2. For lymphedema, certain measures can reduce extremity volume and slow disease progression, such as exercise, maintenance of normal body mass index, elevation of an affected limb, and use of custom-fitted compression garments (see Section 2.6). Surgical intervention for lymphedema is a consideration if conservative management fails (Greene et al., 2020).

In general, the primary care physician plays a critical role in assessing caregiver abilities, socioeconomic needs, and the coordination of care among multiple specialists and therapists. Not every practice is equally equipped and staffed for patients with complex and/or special needs, and families should discuss practice capacity in advance. A "medical home" model is desirable; where available, "complex care" physicians and practices with enhanced access to resources such as care coordinators, social work, and home care should be considered.

2.6 | Physiatry

2.6.1 | Spectrum of neuromuscular and mobility impairments

Individuals with PMS can experience significant neuromuscular impairments and decreased mobility. In a review of clinical data from 17 individuals with PMS evaluated by physicians and therapists at the NIH Clinical Center Rehabilitation Medicine Department, common challenges included joint hypermobility, often generalized but with notable pes planovalgus, and difficulty running more than 150 yards (137 m). Features which were less common but still present were genu valgus (likely secondary to the pes planovalgus), frequent falls, and difficulty walking more than 1 mi (1.6 km), and leg length discrepancies (unpublished data). The mechanisms underlying this motor dysfunction are unclear, but joint hypermobility may suggest connective tissue pathology as one possible contributing factor (Geuze, 2005; Johnston et al., 2002); another contributing factor may be the fact that SHANK3 plays a role in the maturation of neuromuscular junctions and striated muscle (Lutz et al., 2020; Raab et al., 2010).

Recommendations (Table 7).

Surveillance to identify physical impairments. We recommend annual evaluations with a physiatrist, if feasible. When there is no available physiatrist, other specialists such as developmental pediatricians or orthopedists may be able to play this role, in consultation with a remotely available pediatric physiatrist. Examination should include assessment of (1) range of motion and alignment, (2) spinal asymmetry and pelvic obliquity, and (3) leg length discrepancy. If there is a concerning clinical finding, imaging (plain radiographs in most cases) can verify the finding and assess its severity. We recommend monitoring gait efficiency (e.g., speed, cadence, symmetry, and step/stride length) and stability; assessing reach and grasp; and assessing for lymphedema in both upper and lower limbs.

TABLE 7 Recommendations pertaining to physiatry considerations in Phelan–McDermid syndrome (PMS).

Domain	Recommendations
Screening/ surveillance	Consider evaluation by physiatry at the time of diagnosis and annually, if feasible
	Annual assessment should evaluate range of motion and alignment; spinal asymmetry and pelvic obliquity; and leg length discrepancy
	Physiatry can monitor gait efficiency (e.g., speed, cadence, symmetry, step/stride length) and stability; assess reach and grasp; and assess for lymphedema in upper and lower limbs
Helpful equipment	Depending on the motor impairment in the individual, consider orthoses for the upper and/or lower extremities to improve function
	In individuals with significant swelling due to lymphedema, consider compression garments, massage, and sequential pumps
	Consider mobility equipment (e.g., adaptive strollers) if needed as soon as the person is beginning to outgrow a standard infant/toddler stroller
Therapeutic interventions	Physical therapy (PT) should focus on gross motor activities which promote strength and improve reaction time
	Other modalities which improve gross motor skills include aquatherapy, hippotherapy, and use of adaptive tricycles
	Occupational therapy (OT) should focus on fine motor activities which improve strength, wrist and hand alignment, and reaction time
	In a school setting, PT and OT should address musculoskeletal impairments and physical disabilities that impact education and performance

Equipment. Depending on the motor impairment in the individual, we recommend considering orthoses for the upper and/or lower extremities to improve function. It is important to minimize the level of bracing, given that individuals with PMS can have sensory integration challenges that may impact their ability to tolerate high contact, restrictive orthoses. In the upper limbs, if there are indications of immature and/or overly tense grasp, we recommend considering soft neoprene wrist hand orthoses. If these are insufficient, a minimal rigid orthosis, such as a thumb spica, may be a suitable alternative. In the lower limbs, we recommend considering shoe insert (plantar contact) orthoses to address foot and ankle misalignment once the individual is reliably bipedal. If plantar contact orthoses are insufficient to achieve functional goals, then minimum rigid orthoses (supramalleolar orthoses or University of California-Berkeley Lab [UCBL] orthoses) are alternatives. A certified orthotist or pedorthist can make custom adaptations to prefabricated orthoses made in neutral alignment. However,

it may be difficult to obtain accurate molds for custom-molded orthoses due to cognitive, behavioral, and/or sensory issues interfering with the acquisition of the mold.

We recommend mobility equipment (e.g., adaptive strollers) if needed to facilitate long-distance mobility as soon as the person is beginning to outgrow a standard infant/toddler stroller. This type of equipment eases the burden on parents/caregivers.

Therapeutic interventions. Different types of developmental therapies may be helpful for individuals with PMS. PT should focus on gross motor activities which promote strength and improve reaction time. Examples of other modalities which improve gross motor skills include aquatherapy, hippotherapy, and use of adaptive tricycles. Occupational therapy (OT) should focus on fine motor activities which improve strength, wrist and hand alignment, and reaction time.

In individuals with significant swelling due to lymphedema, consider compression garments, massage, and sequential pumps. Choosing an appropriate therapy must account for issues of tolerance to tactile stimuli. Serial measurement of limb volume (circumferential tape measure, perometry, or bioimpedance) can help track effectiveness of the chosen therapy for lymphedema.

In a school setting, PT and OT should address musculoskeletal impairments and physical disabilities that impact education and performance. Establishing and addressing these goals in the school setting is required by the Individuals with Disabilities Education Act (IDEA) in the United States.

2.7 | Nephrology and urology

2.7.1 | Spectrum of renal and genitourinary issues

The most common nonstructural genitourinary abnormality is delayed or persistent incontinence, common in PMS (Hussong et al., 2020; Witmer et al., 2019). Individuals with large chromosomal deletions may be more likely to have urinary or bowel incontinence compared with those with small chromosomal deletions (Witmer et al., 2019). The degree to which incontinence in PMS might be a nonspecific feature common among individuals with neurodevelopmental disorders (von Gontard, 2013; von Gontard et al., 2015) is unclear, although general therapeutic and practical approaches will be similar.

Structural renal abnormalities and genitourinary problems are relatively common in PMS, with rates reported as high as 38% (Soorya et al., 2013). However, few studies have systematically examined the prevalence of these problems, and none have used prospective methods. On a comprehensive review of medical records from 32 patients in one study, renal abnormalities included vesicoureteral reflux (13%), hydronephrosis (13%), renal agenesis (6%), dysplastic kidney (3%), and horseshoe kidneys and pyelectasis (3%) (Soorya et al., 2013). Another study documented renal problems in 39 of 148 cases (26%), including vesicoureteral reflux (14%), frequent urinary tract infections (8%), polycystic kidney (5%), duplicated kidney (1%), and dilated renal pelvis (5%); some of the renal problems remained unspecified because in 19% of the cases, the kidney problem was unclassified ("other") whether alone or in combination with a different (specified) kidney problem (Sarasua et al., 2014). A third study on ring chromosome 22 specifically reported that 17% of the cohort had renal abnormalities in the context of genitourinary abnormalities, including neonatal urinary infection and malformed clitoris, vesicoureteral reflux, unilateral multicystic kidney, and "partial renal failure" of unknown cause (Jeffries et al., 2005). There is at least one report of an affected child with a unilateral multicystic kidney and Wilms' tumor in the contralateral, unaffected kidney, as detected with prenatal ultrasound (Kirkpatrick & El-Khechen, 2011).

Anecdotal evidence from PMS parent groups, albeit outside published literature, suggests that other abnormalities may occur. There are reports of hypospadias, persistent urinary leakage beyond incontinent voiding, kidney stones, urinary retention, and neurogenic bladder with need for intermittent urinary catheterization.

Recommendations (Table 8).

At the time of diagnosis, all individuals with PMS should undergo blood pressure measurement and a complete physical exam (including evaluation of the external genitourinary tract). At the time of diagnosis, affected individuals should also undergo renal and bladder sonography. Fetal sonography should not serve as a substitute for a postnatal study, since renal development may be incomplete depending on the age of the fetal ultrasound and since resolution is better with a direct study of the affected individual. Historical observation data suggest that those with *SHANK3* sequence variants or small

TABLE 8 Recommendations pertaining to renal and genitourinary considerations in Phelan–McDermid syndrome.

Domain	Recommendations
Screening/ surveillance	At the time of diagnosis, perform a complete physical exam (including evaluation of the external genitourinary tract) and blood pressure measurement
	At the time of diagnosis, perform renal and bladder sonography
	If any of the diagnostic screening tests are abnormal, refer to pediatric nephrology and/or urology for monitoring or treatment
General	Consider vesicoureteral reflux if there is urinary tract infection at a young age or recurrent urinary tract infections
	If there are urinary symptoms beyond periodic incontinence that develop over time—such as "dribbling," signs of urinary retention, or difficulty voiding—perform *repeat* renal and bladder sonography and refer to nephrology or urology
	Family and primary care team should have communication in advance with the specialist prior to the appointment, given that the genitourinary system is a physically and emotionally sensitive area

deletions involving only *SHANK3* are not likely to have a clinically relevant renal or bladder abnormality at birth. Thus, in the future, it may be possible to revise this recommendation for that specific subgroup of patients with PMS if active screening programs support that observation.

Regardless of genetic findings and despite a normal baseline renal and bladder ultrasound, it is possible that renal/urological pathology could exist or emerge at a later time. For example, renal and bladder sonography may be normal in the setting of vesicoureteral reflux; therefore, urinary tract infection at a young age or recurrent urinary tract infections (UTIs) should prompt consideration of this diagnosis. Urinary symptoms beyond periodic incontinence that develop over time—such as "dribbling," signs of urinary retention, or difficulty voiding—should prompt *repeat* renal and bladder sonography and referral to nephrology or urology.

If any of the diagnostic screening tests are abnormal, then we recommend referral to a pediatric nephrologist and/or urologist for monitoring or treatment. Blood tests (e.g., urea, creatinine, and electrolytes) may be indicated for those individuals with identified renal anomalies or bladder/voiding dysfunction, as these conditions may lead to reduced renal function. Attention to the ability of the individual to empty the bladder and void spontaneously is important, as is attention to constipation, which is commonly associated with voiding dysfunction. Specific review of urinary continence, hygiene, and presence/absence of UTIs between visits is advised.

The genitourinary system is a physically and emotionally sensitive area, and its assessment adds to the existing stress of a medical visit. Therefore, we recommend communication in advance by the family and primary care team to the specialist. Ideally, this approach will help organize information, guide any evaluations that can occur before the visit, and enable the best possible experience during the visit itself.

2.8 | Endocrinology

2.8.1 | Short and tall stature

Growth is the most studied endocrine aspect of PMS. Up to 18% (Sarasua et al., 2014) of individuals with PMS have a history of low birth weight (<2.5 kg). The prevalence of short stature (<5th percentile) and tall stature (>95th percentile) is up to 13% and 31%, respectively (Nevado et al., 2022; Rollins et al., 2011; Soorya et al., 2013). There is a trend of decreasing stature with advancing age (Sarasua et al., 2014; Rollins et al., 2011). One study reported that tall stature was more common in children younger than 10 years (13%, 9/71) versus older than 10 years of age (0%) (Sarasua et al., 2014).

Recommendations (Table 9).

An accurate assessment of growth parameters and growth trajectory is essential. We recommend obtaining and recording gestational age, birth weight, birth length, and birth head circumference. For longitudinal assessments of length and height, appropriate measuring devices (such as a stadiometer) should be used. We recommend monitoring height, weight, and body mass index using standard growth curves (such as those from the US Centers for Disease Control). If there are concerns about growth (short or tall stature), then referral to an endocrinologist is indicated.

TABLE 9 Recommendations pertaining to endocrine considerations in Phelan–McDermid syndrome.

Domain	Recommendations
Screening/surveillance	At the time of diagnosis, note gestational age, birth weight, birth length, and birth head circumference If newborn screening did not occur, test thyroid function to establish a baseline; otherwise, thyroid function tests are only needed if clinically indicated
Short/tall stature	Assess length and height using appropriate measuring devices such as a stadiometer Monitor height, weight, and body mass index using standard growth curves (e.g., from the Centers for Disease Control) Refer to endocrinology if there are concerns about growth (short or tall stature)
Precocious/delayed puberty and other hormonal findings	Refer to endocrinology if there are concerns about precocious or delayed puberty

2.8.2 | Hypothyroidism

Hypothyroidism occurs in 3%–6% of individuals with PMS (Sarasua et al., 2014; Soorya et al., 2013), but more studies are needed to clarify if this risk is increased compared with that of the general population. There are no reports of children younger than 5 years of age with PMS and hypothyroidism, suggesting that congenital hypothyroidism may not be common. There is a report of one individual with PMS and hyperthyroidism (Sarasua et al., 2014).

Recommendations (Table 9).

Newborn screening plays a crucial role in diagnosing congenital hypothyroidism, including in those with PMS. If newborn screening did not occur, we recommend thyroid function tests upon initial diagnosis of PMS. Otherwise, we suggest considering thyroid function tests when clinically indicated.

2.8.3 | Precocious/delayed puberty and other hormonal findings

In one cohort, 12% of cases had central precocious puberty (CPP), more frequently in females (Sarasua et al., 2014). There are no reports in the literature of PMS-associated delayed puberty. There are rare reports of

PMS associated with hypoglycemia of unclear etiology (De Rubeis et al., 2018), diabetes mellitus (Bonaglia et al., 2011; Sarasua et al., 2014), and central diabetes insipidus (Barakat et al., 2004).

Recommendations (Table 9).

It is important to monitor and record appearance of pubertal signs (acne, body odor, axillary and pubic hair, breast development in girls, and testicular volume in boys) and age at menarche. Recording these data will allow the correlation of pubertal events with linear growth data. If there are concerns about precocious or delayed puberty, referral to an endocrinologist is warranted. Evaluation for hypoglycemia, diabetes mellitus, and central diabetes insipidus is based on clinical symptoms.

2.9 | Cardiology

2.9.1 | Spectrum of cardiovascular issues

Knowledge about cardiovascular abnormalities in PMS is limited, as most clinical reports have not included detailed information about cardiovascular structure and function. There are no published data on systematic prospective cardiovascular evaluations in large or longitudinal cohorts of individuals with PMS.

PMS may have variable and nonspecific cardiovascular abnormalities requiring medical and/or surgical intervention. One review of 107 cases from the literature described occasional reports of congenital heart defects, such as patent ductus arteriosus and ventricular septal defect (Cusmano-Ozog et al., 2007). Another review described cardiac abnormalities in >25% of affected individuals (including tricuspid valve regurgitation, atrial septal defect, patent ductus arteriosus, and totally anomalous pulmonary venous connection; Phelan & McDermid, 2012). Among 30 individuals with ring chromosome 22, four (13%) had cardiovascular abnormalities: two with patent ductus arteriosus and two with totally anomalous pulmonary venous connection (Jeffries et al., 2005). In a prospectively ascertained sample of 32 patients with PMS, only one patient had a cardiovascular abnormality (aortic regurgitation; valve morphology not described; Soorya et al., 2013). Recent case reports have reported the following: a 4-month-old girl with PMS secondary to a 22q13.3 deletion who underwent surgical ligation of a patent ductus arteriosus at 3 weeks of age (Kim et al., 2016); a 32-year-old man with PMS who presented with postictal atrial fibrillation (Sanchez-Larsen et al., 2017), a very infrequent cardiac arrhythmia associated with seizures; and a 33-month-old girl with PMS who had one episode of supraventricular tachycardia, progressive dilation of the ascending aorta (Z-score + 4.6) and main pulmonary artery (Z-score + 3), and an aortic root dimension at the upper limit of normal (Deibert et al., 2019).

Recommendations (Table 10).

As part of the initial evaluation in all patients with PMS, we recommend a standard cardiac evaluation, including a detailed physical examination, electrocardiography, and echocardiography. Most, if not all, cardiac defects associated with PMS are congenital. If the initial work-up is unrevealing, subsequent work-ups are only necessary if there are clinical changes.

TABLE 10 Recommendations pertaining to cardiovascular considerations in Phelan–McDermid syndrome.

Domain	Recommendations
Screening/ surveillance	At the time of diagnosis, refer to cardiology for standard cardiac evaluation (detailed physical examination, electrocardiography, and echocardiography)
	If the initial work-up is unrevealing, subsequent work-ups are only necessary if there are clinical changes

2.10 | Gynecology

2.10.1 | Spectrum of gynecological issues

Individuals with PMS can have reproductive tract conditions commonly seen in their age group but not necessarily specific to the disorder. It is currently unknown if individuals with PMS enter puberty earlier, later, or around the same time as nonaffected peers. In one PMS cohort, 12% of cases had CPP, more frequently in females (Sarasua et al., 2014), and there are no reports of delayed puberty. There is anecdotal evidence that puberty may be associated with worsening of neuropsychiatric symptoms, especially in girls (Kohlenberg et al., 2020). Menstruation can present significant challenges for a person with physical disability and ID (Greenwood & Wilkinson, 2013). Adolescents/adults with PMS may suffer from premenstrual syndrome and dysmenorrhea at similar rates as the general population. As with adolescents/adults with other developmental disabilities, individuals with PMS may have medical causes of menstrual irregularities, including thyroid disease, elevated prolactin levels due to antipsychotic use, and polycystic ovary syndrome in the setting of epilepsy and/or use of certain antiseizure medications. Behavioral and hygiene issues that accompany menstrual periods can cause significant challenges for individuals with ID.

Recommendations (Table 11).

As there is no specific literature regarding gynecologic care for individuals with PMS, we recommend general best practices appropriate for individuals with developmental disabilities. According to the American College of Obstetricians and Gynecologists (ACOG), "optimal gynecologic health care for adolescents with disabilities is comprehensive; maintains confidentiality; is an act of dignity and respect toward the patient; maximizes the patient's autonomy; avoids harm; and assesses and addresses the patient's knowledge of puberty, menstruation, sexuality, safety, and consent. When possible, the patient should have the opportunity to be interviewed in private" (American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care, 2016).

We do not recommend premenarchal suppression of menses. We recommend menstrual suppression if there is a desire to reduce the volume and frequency of menstrual flow (see Table 1 of ACOG guidelines on menstrual suppression; https://www.acog.org/clinical/clinical-guidance/clinical-consensus/articles/2022/09/general-approaches-to-medical-management-of-menstrual-suppression). For premenstrual dysphoric mood and physical discomfort associated with menses, we recommend

consideration of combined hormonal contraceptives (Lete & Lapuente, 2016). If abnormal uterine bleeding is present, we recommend an evaluation for underlying medical causes before initiation of menstrual management. In addition, caution should be exercised with patients taking antiseizure medications, as some decrease the efficacy of oral contraceptives (e.g., carbamazepine, oxcarbazepine, topiramate).

In terms of preventative care, the American Cancer Society's 2020 guidelines state that cervical cancer screening (human papillomavirus [HPV] testing or HPV/Pap cotesting) should occur every 5 years between age 25 and 65 years (Fontham et al., 2020). The Centers for Disease Control recommends HPV vaccination for males/females at age 11–12 years or at a time-point through age 26 years if they have not received adequate vaccination previously (Meites et al., 2019).

2.11 | Dentistry

2.11.1 | Spectrum of dental issues

Medical and behavioral features associated with PMS can have ramifications for dental care. Hypotonia, commonly observed in PMS (Kolevzon, Angarita, et al., 2014), may affect chewing muscles. As a result, affected individuals may have issues with drooling, gagging, and swallowing, complicating oral care (Developmental Disabilities & Oral Health | National Institute of Dental and Craniofacial Research, n.d., https://www.nidcr.nih.gov/health-info/developmental-disabilities). GER may cause teeth to become overly sensitive or display signs of erosion (Ranjitkar et al., 2012). During some types of seizures, individuals may chip their teeth or bite their tongue/cheeks (Developmental Disabilities & Oral Health | National Institute of Dental and Craniofacial Research, n.d., https://www.nidcr.nih.gov/health-info/developmental-disabilities). Some of the most commonly reported repetitive behaviors seen in PMS include chewing/mouthing objects and teeth grinding (bruxism), indicating a possible need for oral intervention (Soorya et al., 2013).

Individuals with PMS can also have dental challenges that are common across the neurodevelopmental disability spectrum, including tooth decay, periodontal disease, malocclusion, delayed tooth eruptions, oral trauma/injury, and various oral malformations (Developmental Disabilities & Oral Health | National Institute of Dental and Craniofacial Research, n.d., https://www.nidcr.nih.gov/health-info/developmental-disabilities). As with other children with developmental disabilities (Norwood et al., 2013), some of the risk factors that place individuals with PMS at greater risk of developing dental diseases include dependence on a caregiver for oral hygiene; behavioral challenges preventing oral hygiene; impaired salivary function resulting in xerostomia due to use of certain medications, and the use of medications high in sugar content, increasing risk of tooth decay.

Difficulty in receiving consistent and comprehensive oral care may be a critical barrier for individuals with PMS. According to the American Academy of Pediatric Dentistry (AAPD), many dentists are less willing to treat patients with special needs due to their complicated health histories, decreased neuromotor control, requirement for increased appointment and procedure time, and possible need for sedation and anesthesia for dental care (American Academy of Pediatric Dentistry, 2022b). According to the National Survey of Children with Special Health Care Needs, dental care is one of the most common unmet areas for children with special needs (U.S. Department of Health and Human Service, Health Resources and Service Administration, Maternal and Child Health Bureau, 2013).

Recommendations (Table 12).

Reducing the risk of developing oral disease is an integral part of comprehensive oral healthcare for individuals with PMS. The AAPD publishes best practices and clinical guidelines related to the management of dental patients with special healthcare needs. These recommendations outline important components of dental care such as establishment of a dental home, patient assessment, appointment scheduling,

TABLE 11 Recommendations pertaining to gynecological considerations in Phelan–McDermid syndrome.

Domain	Recommendations
Screening/ surveillance	Screening for cervical cancer (human papillomavirus [HPV] testing or HPV/Pap co-testing) should occur every 5 years between ages 25–65 years
	HPV vaccination should occur at age 11–12 years, or at a time point through age 26 years if there is inadequate previous vaccination
General	If abnormal uterine bleeding is present, evaluate for underlying causes before initiation of menstrual management
	We do not recommend premenarchal suppression of menses
	Consider menstrual suppression if there is a desire to reduce the volume and frequency of menstrual flow
	Consider combined hormonal contraceptives for premenstrual dysphoric mood and physical discomfort associated with menses

TABLE 12 Recommendations pertaining to dentistry considerations in Phelan–McDermid syndrome (PMS).

Domain	Recommendations
Screening/ surveillance	Establish a dental home during the first year of age, no later than 6 months after the first tooth erupts
	Schedule routine dental visits every 6 months, or sooner, depending on the child's the risk of developing cavities or gum disease
General	Use fluoridated toothpaste daily
	Provide education on dietary/medication considerations (such as medications with high sugar content) and oral habits (such as bruxism)
	Discuss treatment strategies for dental care, including behavior guidance and options for treatment in a hospital setting with deep sedation or general anesthesia

TABLE 13 Definitions of commonly used genetics terms.

Term	Definition
Aneuploidy	A condition in which the total number of chromosomes in a cell is not the typical number (e.g., 45 chromosomes instead of 46 in a human cell)
Autosomal	Pertaining to chromosomes 1–22 and not to the X or Y chromosome
Autosomal dominant	An autosomal mode of inheritance of a genetic condition in which only one copy of a gene must be abnormal for a condition to manifest
Autosomal recessive	An autosomal mode of inheritance of a genetic condition in which both copies of a gene must be abnormal for a condition to manifest
Balanced chromosomal rearrangement	Chromosomal rearrangement (see definition) in which the total amount of DNA is the same (i.e., there is no net gain or loss of genetic material)
Chromosomal inversion	Chromosomal rearrangement in which a portion of one chromosome inverts (rotates 180 degrees)
Chromosomal microarray	A test that uses binding of probes (DNA fragments arranged on a chip) to detect deletions or duplications of chromosomal material at a higher resolution than that of fluorescence in situ hybridization or karyotype
Chromosomal rearrangement	Alteration in the chromosomal material in which parts of chromosomal material are deleted (missing), duplicated (extra), inverted (rotated 180 degrees), or translocated (exchanged or shifted from one chromosome to another)
Chromosomal translocation	Chromosomal rearrangement in which part of a chromosome becomes incorporated into another chromosome
De novo	Inheritance status of a variant indicating that it is present in an individual but not in either parent
Exome sequencing	A type of next-generation sequencing (see definition) involving sequencing the coding portions (exons) of all genes within the genome (i.e., exome)
Fluorescence in situ hybridization	A test that uses fluorescent probes to bind to chromosomes to assess for the presence, absence, and position of specific DNA regions
Genome sequencing	A type of next-generation sequencing (see definition) involving sequencing the coding and noncoding portions of all genes and the regions between genes (i.e., genome)
Gonadal mosaicism (also known as germline mosaicism)	A state in which a variant is present in either sperm or egg cells, but not in other tissue types
Haploinsufficiency	A state in which loss of function of one copy of a gene or genetic region is sufficient to cause symptoms of a genetic disorder
Interstitial deletion	A chromosomal deletion within the interior of a chromosome
Karyotype	A test that using a microscope to visualize the size, shape, and number of chromosomes in an individual
Mosaic aneuploidy	Aneuploidy (see definition) which affects some cells, but not every cell, in the body
Next-generation sequencing	Term used for sequencing of DNA that involves sequencing many DNA targets in parallel, in contrast to traditional (Sanger) sequencing which involves sequencing one DNA target at a time
Ring chromosome	A circular structure formed when the distal long arm and the distal short arm of a chromosome truncate and join
Sequence variant	A change in the DNA sequence within a gene, involving one or several nucleotides, manifesting as substitutions of one nucleotide for another; deletion of one or more nucleotides; duplication of one or more nucleotides; insertion of one or more nucleotides; or deletion of one or more nucleotides and replacement by new nucleotides
Somatic variant	A variant that is present in some cells, but not all cells, in the body
Terminal deletion	A chromosomal deletion including the end of a chromosome
Unbalanced chromosomal rearrangement	Chromosomal rearrangement in which there is a net gain or loss of total chromosomal material
Variable expressivity	Variability in the severity/range of symptoms of those who have a genetic disorder
Variant of uncertain significance	A classification of the pathogenicity of a variant in which there is uncertainty about whether the variant is causative of the condition

medical considerations, dental treatment planning, informed consent, behavior guidance, preventive treatment strategies, barriers, referrals, and transition to adult dentistry (American Academy of Pediatric Dentistry, 2022a). We have largely adapted these recommendations here.

We recommend establishing a dental home, with the first visit to a dentist by 1 year of age and no later than 6 months after the first tooth erupts. This visit will help the dentist discuss how to keep the child's teeth as healthy as possible and what to expect in individuals

with PMS. It is important to establish preventive strategies for daily oral hygiene at home that accommodate the abilities of both the patient and the caregiver. We recommend daily use of fluoridated toothpaste. We recommend providing oral health education and anticipatory guidance pertaining to dietary/medication considerations (such as medications with high sugar content) and oral habits (such as bruxism). We recommend scheduling routine dental visits every 6 months or sooner depending on the child's risk for developing cavities or gum disease. We recommend obtaining dental radiographs when clinically appropriate for the child. We recommend providing treatment strategies for dental care, including behavior guidance as well as options for treatment in a hospital setting able to provide procedural sedation or general anesthesia.

3 | CONCLUSIONS

In this report, we have provided updated consensus guidelines for the management of PMS, spanning the domains of genetics, neurology, neurodevelopment, gastroenterology, primary care, physiatry, nephrology, endocrinology, cardiology, gynecology, and dentistry.

From a genetics standpoint, there are now known genotype–phenotype correlations where deletions of genes other than *SHANK3* may be associated with some medical features, including renal/urinary tract abnormalities and lymphedema. Moreover, the severity of neurodevelopmental impairment appears to correlate with a larger deletion size. PMS is only diagnosed through genetic testing, with pretest and posttest genetic counseling recommended. Following the identification of a pathogenic variant or a VUS in a patient, parental testing is recommended. The results of parental testing can aid in the assessment of VUS and inform genetic counseling. When PMS occurs as the result of a ring chromosome 22, additional surveillance screening is recommended.

From a neurology standpoint, seizures occur in ~1/3 of individuals with PMS and warrant evaluation with EEG and neuroimaging, preferably using MRI. No particular anti-seizure medication has been identified to have superior efficacy in PMS; therefore, choice of medication should be based upon seizure semiology. Individuals with a ring chromosome 22 are at risk for the development of NF2 and should have routine neuroimaging every 1–2 years starting at 10 years of age to evaluate for vestibular schwannomas or other intracranial tumors. Autoimmune encephalitis might be a rare complication in PMS that leads to behavioral changes or developmental regression and should be considered in such individuals.

From a neurodevelopmental standpoint, there is a wide spectrum of neurodevelopmental challenges, including ID, impaired communication, behavioral challenges, sleep difficulties, and psychiatric symptoms. Major behavioral and emotional changes including disabling anxiety, mood cycling, psychosis, catatonia, and loss of skills can occur in adolescence and adulthood. Because of the vulnerability to adverse effects of several commonly used groups of psychiatric medications, the treatment recommendations from the PMS Neuropsychiatric Consultation Group and guidance from the PMS Foundation Medical Advisory Committee should be considered before psychiatric medications are prescribed. Interventions include direct services (such as with speech and language pathologists and ABA providers), appropriate educational accommodations, and pharmacological treatment if needed. Further research into sex-based differences in psychiatric symptoms with onset around puberty is needed.

From a GI perspective, functional GI disorders are common and may be related to enteric nervous system and pelvic floor dysfunction from *SHANK3* disruption. Earlier referral and more aggressive therapy may be necessary in PMS.

From a primary care standpoint, individuals with PMS are at increased risk for a variety of primary care concerns and require increased vigilance and screening for vision issues, hearing issues, thermoregulation challenges, infections, and skin issues. Families should assess the capacity and availability of practices in advance, as not every practice is equipped for patients with special needs. If feasible, a "medical home" model is ideal, wherein "complex care" physicians, care coordinators, social workers, and home-based care may be available.

From a physiatry standpoint, individuals with PMS manifest impairments in musculoskeletal and lymphatic function which can impact mobility and self-care. Function can be improved and optimized by early involvement of a physical rehabilitation team using therapy, orthoses, and rehabilitation devices. Ideally, the rehabilitation team should include a physiatrist, occupational therapist, and physical therapist, in addition to existing providers like speech and language pathologists. Where a physiatrist is unavailable, a neurodevelopmental pediatrician or pediatric orthopedist could fill the physiatrist's role, ideally in consultation with a physiatrist.

From a nephrology perspective, individuals with PMS can be affected with structural and functional renal/bladder abnormalities warranting baseline screening with renal and bladder sonography. Depending on the abnormalities identified, further evaluation with a nephrologist and/or urologist may be needed.

Endocrine features of PMS can encompass growth issues, thyroid dysfunction, and abnormal pubertal onset. Concerns about these areas would warrant a timely referral to endocrinology.

From a cardiology perspective, cardiovascular abnormalities are mostly congenital and occur in a minority of individuals. A baseline cardiovascular evaluation is recommended, and most individuals with PMS do not require long-term cardiology care.

Affected individuals should receive gynecological care in accordance with general best practices appropriate for individuals with developmental disabilities, per the ACOG.

Regarding dentistry needs, individuals with PMS can be at higher risk for dental problems due to underlying medical issues, similar to other neurodevelopmental disorders. Management of dental needs should be in accordance with best practices and guidelines published by the AAPD.

These updated consensus guidelines represent an advance for the field and will improve care for affected individuals and their families in the community. Nevertheless, significant gaps in knowledge remain and may be addressed by ongoing studies using deep phenotyping and carefully tracking the natural history of the syndrome.

The guidelines developed here are relevant to individuals who have involvement of *SHANK3* and thus do not necessarily apply to those without *SHANK3* haploinsufficiency; more efforts are needed to better understand the phenotypic impact of other genes in the 22q13 region.

Biomarker studies using EEG and other technology may be especially helpful for understanding the clinical heterogeneity. Several converging and ongoing areas of research are dedicated to clinical trial readiness as more potential treatments become worthy of testing in randomized, controlled, multicentered trials. In addition, as knowledge about genotype–phenotype relationships deepens, future guidelines will provide more practical information about course of illness and enhance genetic counseling efforts. With additional research, subsequent updates to these guidelines will provide more refined and specific recommendations for the PMS community.

AUTHOR CONTRIBUTIONS

Alexander Kolevzon conceptualized and designed the study; co-chaired the taskforce to update the guidelines; and drafted and edited a significant portion of the article. Siddharth Srivastava co-chaired the taskforce to update the guidelines; drafted and edited a significant portion of the article. The remaining authors contributed to intellectual content contained in the guidelines and drafted or edited a significant portion of the article.

AFFILIATIONS

[1]Department of Neurology, Boston Children's Hospital, Boston, Massachusetts, USA
[2]Rosamund Stone Zander Translational Neuroscience Center, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[3]Seaver Autism Center for Research and Treatment, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[4]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[5]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[6]Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[7]Department of Pediatrics, Rush University Medical Center, Chicago, Illinois, USA
[8]Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA
[9]Department of Biochemistry, Rush University Medical Center, Chicago, Illinois, USA
[10]Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, Illinois, USA
[11]Neurodevelopmental and Behavioral Phenotyping Service, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA
[12]Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA
[13]Rehabilitation Medicine Department, NIH Clinical Center, Bethesda, Maryland, USA
[14]Department of Pediatrics, Indiana University School of Medicine, Indianapolis, Indiana, USA
[15]Sorbonne Université, INSERM, CNRS, Neuroscience Paris Seine, Institut de Biologie Paris Seine, Paris, France
[16]Department of Dental Public Health & Policy, School of Dentistry, Virginia Commonwealth University, Richmond, Virginia, USA
[17]Departamento de Genética e Biologia Evolutiva, Centro de Estudos do Genoma Humano e Células-tronco, Instituto de Biociências, Universidade de São Paulo, São Paulo, Brazil
[18]Division of Developmental Medicine, Department of Pediatrics, Riley Children's Health, Indianapolis, Indiana, USA
[19]Division of Child Neurology, Department of Neurology, Riley Children's Health, Indianapolis, Indiana, USA
[20]Department of Pediatrics, College of Medicine and Division of Dentistry and Orthodontics, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[21]Indiana University, Indianapolis, Indiana, USA
[22]Department of Pediatrics-Neurology, Baylor College of Medicine, Houston, Texas, USA
[23]Joe DiMaggio Children's Hospital, Hollywood, Florida, USA
[24]Department of Pediatric Dentistry, School of Dentistry, Texas A&M University, Dallas, Texas, USA
[25]National Institute of Neurological Disease and Stroke, Bethesda, Maryland, USA
[26]University of Massachusetts Chan Medical School, Worcester, Massachusetts, USA
[27]Department of Cardiology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA
[28]University of Southern California, Arcadia, California, USA
[29]Phelan-McDermid Syndrome Foundation, Osprey, Florida, USA
[30]Kings College London, London, UK
[31]Department of Medicine, Wake Forest/Atrium Health, Charlotte, North Carolina, USA
[32]Lurie Center for Autism, Massachusetts General Hospital, Lexington, Massachusetts, USA, Harvard Medical School, Boston, Massachusetts, USA
[33]Genetics Laboratory, Florida Cancer Specialists and Research Institute, Fort Myers, Florida, USA
[34]Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy
[35]Department of Pediatrics, Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[36]RCR Genetics, Greer, South Carolina, USA
[37]Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts, USA
[38]Access Behavior Analysis, Indianapolis, Indiana, USA
[39]Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA
[40]Department of Medical and Molecular Genetics, Riley Children's Health, Indianapolis, Indiana, USA
[41]Sinai Rehabilitation Center, Lifebridge Health, Baltimore, Maryland, USA
[42]Department of Pediatrics, The Ohio State University School of Medicine, Columbus, Ohio, USA

[43]Emerson Health, Concord, Massachusetts, USA
[44]Massachusetts General Hospital, Boston, Massachusetts, USA

ACKNOWLEDGMENTS

The Developmental Synaptopathies Consortium (U54NS092090) is part of the Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS). Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (NINDS), Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD), National Institute of Mental Health (NIMH), and National Center for Advancing Translational Sciences (NCATS). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH). Siddharth Srivastava is funded by NIH National Institute of Neurological Disorders and Stroke (K23NS119666). We would like to thank the families and the Phelan–McDermid Syndrome Foundation and all national Phelan–McDermid Syndrome family associations throughout the world.

CONFLICT OF INTEREST STATEMENT

Siddharth Srivastava has received consulting fees from GLG, Guidepoint (which connected to a client, Fortress Biotech), Novartis, ExpertConnect, Orchard Therapeutics, and Stoke Therapeutics. Alexander Kolevzon is on the Advisory Board for the Klingenstein Third Generation Foundation, Ovid Therapeutics, David Lynch Foundation, ADNP Kids Research Foundation, and Ritrova Therapeutics and consults to Acadia, Alkermes, Jaguar Therapeutics, GW Pharmaceuticals, Neuren Pharmaceuticals, Clinilabs Drug Development Corporation, Scioto Biosciences, and Biogen. Mustafa 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.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Siddharth Srivastava https://orcid.org/0000-0001-7008-1879
Jonathan A. Bernstein https://orcid.org/0000-0001-5369-346X

REFERENCES

Ahn, H., Seo, G. H., Keum, C., Heo, S. H., Kim, T., Choi, J., Yum, M.-S., & Lee, B. H. (2020). Diagnosis of metachromatic leukodystrophy in a patient with regression and Phelan-McDermid syndrome. *Brain Development*, *42*, 414–417.

American Academy of Pediatric Dentistry. (2022a). Management of dental patients with special health care needs. In *The reference manual of pediatric dentistry* (pp. 302–329). American Academy of Pediatric Dentistry.

American Academy of Pediatric Dentistry. (2022b). Policy on third-party reimbursement for management of patients with special health care needs. In *The reference manual of pediatric dentistry* (pp. 152–155). American Academy of Pediatric Dentistry.

Anonymous. (2018b). Policy on third-party reimbursement for Management of Patients with special health care needs. *Pediatric Dentistry*, *40*, 114–116.

Ardern-Holmes, S., Fisher, G., & North, K. (2017). Neurofibromatosis type 2: Presentation, major complications, and management, with a focus on the pediatric age group. *Journal of Child Neurology*, *32*, 9–22.

Barakat, A. J., Pearl, P. L., Acosta, M. T., & Runkle, B. P. (2004). 22q13 deletion syndrome with central diabetes insipidus: A previously unreported association. *Clinical Dysmorphology*, *13*, 191–194.

Bartsch, O., Schneider, E., Damatova, N., Weis, R., Tufano, M., Iorio, R., Ahmed, A., Beyer, V., Zechner, U., & Haaf, T. (2010). Fulminant hepatic failure requiring liver transplantation in 22q13.3 deletion syndrome. *American Journal of Medical Genetics. Part A*, *152A*, 2099–2102.

Bey, A. L., Gorman, M. P., Gallentine, W., Kohlenberg, T. M., Frankovich, J., Jiang, Y., & Haren, K. V. (2020). Subacute Neuropsychiatric Syndrome in Girls With SHANK3 Mutations Responds to Immunomodulation. *Pediatrics*, *145*, e20191490.

Bisgaard, A.-M., Kirchhoff, M., Nielsen, J. E., Kibaek, M., Lund, A., Schwartz, M., & Christensen, E. (2009). Chromosomal deletion unmasking a recessive disease: 22q13 deletion syndrome and metachromatic leukodystrophy. *Clinical Genetics*, *75*, 175–179.

Boccuto, L., Abenavoli, L., Cascio, L., Srikanth, S., DuPont, B., Mitz, A. R., Rogers, R. C., & Phelan, K. (2018). Variability in Phelan-McDermid syndrome: The impact of the PNPLA3 p.I148M polymorphism. *Clinical Genetics*, *94*, 590–591.

Boccuto, L., Lauri, M., Sarasua, S. M., Skinner, C. D., Buccella, D., Dwivedi, A., Orteschi, D., Collins, J. S., Zollino, M., Visconti, P., Dupont, B., Tiziano, D., Schroer, R. J., Neri, G., Stevenson, R. E., Gurrieri, F., & Schwartz, C. E. (2013). Prevalence of SHANK3 variants in patients with different subtypes of autism spectrum disorders. *European Journal of Human Genetics*, *21*, 310–316.

Bonaglia, M. C., Giorda, R., Beri, S., De Agostini, C., Novara, F., Fichera, M., Grillo, L., Galesi, O., Vetro, A., Ciccone, R., Bonati, M. T., Giglio, S., Guerrini, R., Osimani, S., Marelli, S., Zucca, C., Grasso, R., Borgatti, R., Mani, E., … Zuffardi, O. (2011). Molecular mechanisms generating and stabilizing terminal 22q13 deletions in 44 subjects with Phelan/McDermid syndrome. *PLoS Genetics*, *7*, e1002173.

Bonaglia, M. C., Giorda, R., Borgatti, R., Felisari, G., Gagliardi, C., Selicorni, A., & Zuffardi, O. (2001). Disruption of the ProSAP2 gene in a t(12;22)(q24.1;q13.3) is associated with the 22q13.3 deletion syndrome. *American Journal of Human Genetics*, *69*, 261–268.

Bonaglia, M. C., Giorda, R., Mani, E., Aceti, G., Anderlid, B.-M., Baroncini, A., Pramparo, T., & Zuffardi, O. (2006). Identification of a recurrent breakpoint within the SHANK3 gene in the 22q13.3 deletion syndrome. *Journal of Medical Genetics*, *43*, 822–828.

Bosch, A., & Estévez, R. (2020). Megalencephalic leukoencephalopathy: Insights into pathophysiology and perspectives for therapy. *Frontiers in Cellular Neuroscience*, *14*, 627887.

Brignell, A., Gu, C., Holm, A., Carrigg, B., Sheppard, D. A., Amor, D. J., & Morgan, A. T. (2021). Speech and language phenotype in Phelan-McDermid (22q13.3) syndrome. *European Journal of Human Genetics*, *29*, 564–574.

Bro, D., O'Hara, R., Primeau, M., Hanson-Kahn, A., Hallmayer, J., & Bernstein, J. A. (2017). Sleep disturbances in individuals with Phelan-McDermid syndrome: Correlation with Caregivers' sleep quality and daytime functioning. *Sleep*, *40*, 28364490.

Burdeus-Olavarrieta, M., San José-Cáceres, A., García-Alcón, A., González-Peñas, J., Hernández-Jusdado, P., & Parellada-Redondo, M. (2021). Characterisation of the clinical phenotype in Phelan-McDermid syndrome. *Journal of Neurodevelopmental Disorders*, *13*, 26.

Byers, H. M., Adam, M. P., LaCroix, A., Leary, S. E. S., Cole, B., Dobyns, W. B., & Mefford, H. C. (2017). Description of a new oncogenic mechanism for atypical teratoid rhabdoid tumors in patients with

ring chromosome 22. *American Journal of Medical Genetics. Part A*, *173*, 245–249.

Cho, E. H., Park, J. B., & Kim, J. K. (2014). Atypical teratoid rhabdoid brain tumor in an infant with ring chromosome 22. *Korean Journal of Pediatrics*, *57*, 333–336.

Cusmano-Ozog, K., Manning, M. A., & Hoyme, H. E. (2007). 22q13.3 deletion syndrome: A recognizable malformation syndrome associated with marked speech and language delay. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*, *145C*, 393–398.

Dawson, G., Rogers, S., Munson, J., Smith, M., Winter, J., Greenson, J., Donaldson, A., & Varley, J. (2010). Randomized, controlled trial of an intervention for toddlers with autism: The early start Denver model. *Pediatrics*, *125*, e17–e23.

De Rubeis, S., He, X., Goldberg, A. P., Poultney, C. S., Samocha, K., Cicek, A. E., Kou, Y., Liu, L., Fromer, M., Walker, S., Singh, T., Klei, L., Kosmicki, J., Shih-Chen, F., Aleksic, B., Biscaldi, M., Bolton, P. F., Brownfeld, J. M., Cai, J., … Buxbaum, J. D. (2014). Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature*, *515*, 209–215.

De Rubeis, S., Siper, P. M., Durkin, A., Weissman, J., Muratet, F., Halpern, D., Trelles, M. D. P., Frank, Y., Lozano, R., Wang, A. T., Holder, J. L., Betancur, C., Buxbaum, J. D., & Kolevzon, A. (2018). Delineation of the genetic and clinical spectrum of Phelan-McDermid syndrome caused by SHANK3 point mutations. *Molecular Autism*, *9*, 31.

Deibert, E., Crenshaw, M., & Miller, M. S. (2019). A patient with Phelan-McDermid syndrome and dilation of the great vessels. *Clinical Case Reports*, *7*, 607–611.

Developmental Disabilities & Oral Health | National Institute of Dental and Craniofacial Research. (n.d.).

Dhar, S. U., del Gaudio, D., German, J. R., Peters, S. U., Ou, Z., Bader, P. I., Berg, J. S., Blazo, M., Brown, C. W., Graham, B. H., Grebe, T. A., Lalani, S., Irons, M., Sparagana, S., Williams, M., Phillips, J. A., Beaudet, A. L., Stankiewicz, P., Patel, A., … Sahoo, T. (2010). 22q13.3 deletion syndrome: Clinical and molecular analysis using array CGH. *American Journal of Medical Genetics. Part A*, *152A*, 573–581.

Dhossche, D. M., & Wachtel, L. E. (2010). Catatonia is hidden in plain sight among different pediatric disorders: A review article. *Pediatric Neurology*, *43*, 307–315.

Droogmans, G., Swillen, A., & Van Buggenhout, G. (2020). Deep phenotyping of development, communication and behaviour in Phelan-McDermid syndrome. *Molecular Syndromology*, *10*, 294–305.

Duncan, A., Yacoubian, C., Watson, N., & Morrison, I. (2015). The risk of copper deficiency in patients prescribed zinc supplements. *Journal of Clinical Pathology*, *68*, 723–725.

Durand, C. M., Betancur, C., Boeckers, T. M., Bockmann, J., Chaste, P., Fauchereau, F., Nygren, G., Rastam, M., Gillberg, I. C., Anckarsäter, H., Sponheim, E., Goubran-Botros, H., Delorme, R., Chabane, N., Mouren-Simeoni, M.-C., de Mas, P., Bieth, E., Rogé, B., Héron, D., … Bourgeron, T. (2007). Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nature Genetics*, *39*, 25–27.

Egger, J. I. M., Verhoeven, W. M. A., Groenendijk-Reijenga, R., & Kant, S. G. (2017). Phelan-McDermid syndrome due to SHANK3 mutation in an intellectually disabled adult male: Successful treatment with lithium. *BML Case Reports*, *2017*, bcr2017220778.

Egger, J. I. M., Zwanenburg, R. J., van Ravenswaaij-Arts, C. M. A., Kleefstra, T., & Verhoeven, W. M. A. (2016). Neuropsychological phenotype and psychopathology in seven adult patients with Phelan-McDermid syndrome: Implications for treatment strategy. *Genes, Brain and Behavior*, *15*, 395–404.

Eldevik, S., Hastings, R. P., Hughes, J. C., Jahr, E., Eikeseth, S., & Cross, S. (2009). Meta-analysis of early intensive behavioral intervention for children with autism. *Journal of Clinical Child and Adolescent Psychology*, *38*, 439–450.

Erickson, R. P., Lai, L.-W., Mustacich, D. J., Bernas, M. J., Kuo, P. H., & Witte, M. H. (2019). Sex-limited penetrance of lymphedema to females with CELSR1 haploinsufficiency: A second family. *Clinical Genetics*, *96*, 478–482.

Erland, L. A. E., & Saxena, P. K. (2017). Melatonin natural health products and supplements: Presence of serotonin and significant variability of melatonin content. *Journal of Clinical Sleep Medicine*, *13*, 275–281.

Evans, D. G. (1993). Neurofibromatosis 2. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, G. M. Mirzaa, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle.

Fastman, J., Foss-Feig, J., Frank, Y., Halpern, D., Harony-Nicolas, H., Layton, C., Sandin, S., Siper, P., Tang, L., Trelles, P., Zweifach, J., Buxbaum, J. D., & Kolevzon, A. (2021). A randomized controlled trial of intranasal oxytocin in Phelan-McDermid syndrome. *Molecular Autism*, *12*, 62.

Fontham, E. T. H., Wolf, A. M. D., Church, T. R., Etzioni, R., Flowers, C. R., Herzig, A., Guerra, C. E., Oeffinger, K. C., Shih, Y.-C. T., Walter, L. C., Kim, J. J., Andrews, K. S., DeSantis, C. E., Fedewa, S. A., Manassaram-Baptiste, D., Saslow, D., Wender, R. C., & Smith, R. A. (2020). Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA: A Cancer Journal for Clinicians*, *70*, 321–346.

Francque, S., Vonghia, L., Ramon, A., & Michielsen, P. (2012). Epidemiology and treatment of autoimmune hepatitis. *Hepatic Medicine: Evidence and Research*, *4*, 1–10.

Fu, J. M., Satterstrom, F. K., Peng, M., Brand, H., Collins, R. L., Dong, S., Wamsley, B., Klei, L., Wang, L., Hao, S. P., Stevens, C. R., Cusick, C., Babadi, M., Banks, E., Collins, B., Dodge, S., Gabriel, S. B., Gauthier, L., Lee, S. K., … Talkowski, M. E. (2022). Rare coding variation provides insight into the genetic architecture and phenotypic context of autism. *Nature Genetics*, *54*, 1320–1331.

Gauthier, J., Champagne, N., Lafrenière, R. G., Xiong, L., Spiegelman, D., Brustein, E., Lapointe, M., Peng, H., Côté, M., Noreau, A., Hamdan, F. F., Addington, A. M., Rapoport, J. L., Delisi, L. E., Krebs, M.-O., Joober, R., Fathalli, F., Mouaffak, F., Haghighi, A. P., … S2D Team. (2010). De novo mutations in the gene encoding the synaptic scaffolding protein SHANK3 in patients ascertained for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 7863–7868.

Gauthier, J., Spiegelman, D., Piton, A., Lafrenière, R. G., Laurent, S., St-Onge, J., Lapointe, L., Hamdan, F. F., Cossette, P., Mottron, L., Fombonne, É., Joober, R., Marineau, C., Drapeau, P., & Rouleau, G. A. (2009). Novel de novo SHANK3 mutation in autistic patients. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *150B*, 421–424.

Gergoudis, K., Weinberg, A., Templin, J., Farmer, C., Durkin, A., Weissman, J., Siper, P., Foss-Feig, J., Del Pilar Trelles, M., Bernstein, J. A., Buxbaum, J. D., Berry-Kravis, E., Powell, C. M., Sahin, M., Soorya, L., Thurm, A., Kolevzon, A., & Developmental Synaptopathies Consortium. (2020). Psychometric study of the social responsiveness scale in Phelan-McDermid syndrome. *Autism Research*, *13*, 1383–1396.

Geuze, R. H. (2005). Postural control in children with developmental coordination disorder. *Neural Plasticity*, *12*, 183–196; discussion 263–272.

Gong, X., Jiang, Y.-W., Zhang, X., An, Y., Zhang, J., Wu, Y., Wang, J., Sun, Y., Liu, Y., Gao, X., Shen, Y., Wu, X., Qiu, Z., Jin, L., Wu, B.-L., & Wang, H. (2012). High proportion of 22q13 deletions and SHANK3 mutations in Chinese patients with intellectual disability. *PLoS One*, *7*, e34739.

Gonzalez-Garay, M. L., Aldrich, M. B., Rasmussen, J. C., Guilliod, R., Lapinski, P. E., King, P. D., & Sevick-Muraca, E. M. (2016). A novel mutation in CELSR1 is associated with hereditary lymphedema. *Vascular Cell*, *8*, 1.

Greene, A. K., Sudduth, C. L., & Taghinia, A. (2020). Lymphedema (seminars in pediatric surgery). *Seminars in Pediatric Surgery*, *29*, 150972.

Greenwood, N. W., & Wilkinson, J. (2013). Sexual and reproductive health care for women with intellectual disabilities: A primary care perspective. *International Journal of Family Medicine*, *2013*, 642472.

Hamdan, F. F., Gauthier, J., Araki, Y., Lin, D.-T., Yoshizawa, Y., Higashi, K., Park, A.-R., Spiegelman, D., Dobrzeniecka, S., Piton, A., Tomitori, H., Daoud, H., Massicotte, C., Henrion, E., Diallo, O., S2D Group, Shekarabi, M., Marineau, C., Shevell, M., … Michaud, J. L. (2011). Excess of de novo deleterious mutations in genes associated with glutamatergic systems in nonsyndromic intellectual disability. *American Journal of Human Genetics*, *88*, 306–316.

Hodge, D., Carollo, T. M., Lewin, M., Hoffman, C. D., & Sweeney, D. P. (2014). Sleep patterns in children with and without autism spectrum disorders: Developmental comparisons. *Research in Developmental Disabilities*, *35*, 1631–1638.

Holder, J. L., & Quach, M. M. (2016). The spectrum of epilepsy and electroencephalographic abnormalities due to SHANK3 loss of function mutations. *Epilepsia*, *57*, 1651–1659.

Hussong, J., Wagner, C., Curfs, L., & von Gontard, A. (2020). Incontinence and psychological symptoms in Phelan-McDermid syndrome. *Neurourology and Urodynamics*, *39*, 310–318.

Ingiosi, A. M., Schoch, H., Wintler, T., Singletary, K. G., Righelli, D., Roser, L. G., Medina, E., Risso, D., Frank, M. G., & Peixoto, L. (2019). Shank3 modulates sleep and expression of circadian transcription factors. *eLife*, *8*, e42819.

Jeffries, A. R., Curran, S., Elmslie, F., Sharma, A., Wenger, S., Hummel, M., & Powell, J. (2005). Molecular and phenotypic characterization of ring chromosome 22. *American Journal of Medical Genetics Part A*, *137A*, 139–147.

Johnston, L. M., Burns, Y. R., Brauer, S. G., & Richardson, C. A. (2002). Differences in postural control and movement performance during goal directed reaching in children with developmental coordination disorder. *Human Movement Science*, *21*, 583–601.

Kankuri-Tammilehto, M., Sauna-Aho, O., & Arvio, M. (2021). Neurocognitive follow-up in adult siblings with Phelan-McDermid syndrome due to a novel SHANK3 splicing site mutation. *Molecular Genetics & Genomic Medicine*, *9*, e1780.

Khan, O. I., Zhou, X., Leon, J., Kessler, R., Gaughan, T., D'Souza, P., Gropman, A., Cohen, N., Rennert, O., Buckley, A., Inati, S., & Thurm, A. (2018). Prospective longitudinal overnight video-EEG evaluation in Phelan-McDermid syndrome. *Epilepsy & Behavior*, *80*, 312–320.

Kim, Y.-M., Choi, I.-H., Kim, J. S., Kim, J. H., Cho, J. H., Lee, B. H., Kim, G.-H., Choi, J.-H., Seo, E.-J., & Yoo, H.-W. (2016). Phelan-McDermid syndrome presenting with developmental delays and facial dysmorphisms. *Korean Journal of Pediatrics*, *59*, S25–S28.

Kirkpatrick, B. E., & El-Khechen, D. (2011). A unique presentation of 22q13 deletion syndrome: Multicystic kidney, orofacial clefting, and Wilms' tumor. *Clinical Dysmorphology*, *20*, 53–54.

Kohlenberg, T. M., Trelles, M. P., McLarney, B., Betancur, C., Thurm, A., & Kolevzon, A. (2020). Psychiatric illness and regression in individuals with Phelan-McDermid syndrome. *Journal of Neurodevelopmental Disorders*, *12*, 7.

Kolevzon, A., Angarita, B., Bush, L., Wang, A. T., Frank, Y., Yang, A., Rapaport, R., Saland, J., Srivastava, S., Farrell, C., Edelmann, L. J., & Buxbaum, J. D. (2014). Phelan-McDermid syndrome: A review of the literature and practice parameters for medical assessment and monitoring. *Journal of Neurodevelopmental Disorders*, *6*, 39.

Kolevzon, A., Breen, M. S., Siper, P. M., Halpern, D., Frank, Y., Rieger, H., Weismann, J., Trelles, M. P., Lerman, B., Rapaport, R., & Buxbaum, J. D. (2022). Clinical trial of insulin-like growth factor-1 in Phelan-McDermid syndrome. *Molecular Autism*, *13*, 17.

Kolevzon, A., Bush, L., Wang, A. T., Halpern, D., Frank, Y., Grodberg, D., Rapaport, R., Tavassoli, T., Chaplin, W., Soorya, L., & Buxbaum, J. D. (2014). A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome. *Molecular Autism*, *5*, 54.

Kolevzon, A., Delaby, E., Berry-Kravis, E., Buxbaum, J. D., & Betancur, C. (2019). Neuropsychiatric decompensation in adolescents and adults with Phelan-McDermid syndrome: A systematic review of the literature. *Molecular Autism*, *10*, 50.

Kresbach, C., Dorostkar, M. M., Suwala, A. K., Wefers, A. K., Schweizer, L., Engertsberger, L., Bison, B., Mynarek, M., Kloth-Stachnau, K., Spohn, M., von Deimling, A., Benesch, M., Hagel, C., Mautner, V.-F., Rutkowski, S., & Schüller, U. (2021). Neurofibromatosis type 2 predisposes to ependymomas of various localization, histology, and molecular subtype. *Acta Neuropathologica*, *141*, 971–974.

Lasota, J., Wasag, B., Dansonka-Mieszkowska, A., Karcz, D., Millward, C. L., Ryś, J., Stachura, J., Sobin, L. H., & Miettinen, M. (2003). Evaluation of NF2 and NF1 tumor suppressor genes in distinctive gastrointestinal nerve sheath tumors traditionally diagnosed as benign schwannomas: s study of 20 cases. *Laboratory Investigation*, *83*, 1361–1371.

Leblond, C. S., Nava, C., Polge, A., Gauthier, J., Huguet, G., Lumbroso, S., Giuliano, F., Stordeur, C., Depienne, C., Mouzat, K., Pinto, D., Howe, J., Lemière, N., Durand, C. M., Guibert, J., Ey, E., Toro, R., Peyre, H., Mathieu, A., … Bourgeron, T. (2014). Meta-analysis of SHANK mutations in autism Spectrum disorders: A gradient of severity in cognitive impairments. *PLoS Genetics*, *10*, e1004580.

Lelieveld, S. H., Reijnders, M. R. F., Pfundt, R., Yntema, H. G., Kamsteeg, E.-J., de Vries, P., de Vries, B. B. A., Willemsen, M. H., Kleefstra, T., Löhner, K., Vreeburg, M., Stevens, S. J. C., van der Burgt, I., Bongers, E. M. H. F., Stegmann, A. P. A., Rump, P., Rinne, T., Nelen, M. R., Veltman, J. A., … Gilissen, C. (2016). Meta-analysis of 2,104 trios provides support for 10 new genes for intellectual disability. *Nature Neuroscience*, *19*, 1194–1196.

Lete, I., & Lapuente, O. (2016). Contraceptive options for women with premenstrual dysphoric disorder: Current insights and a narrative review. *Open Access Journal of Contraception*, *7*, 117–125.

Levy, T., Foss-Feig, J. H., Betancur, C., Siper, P. M., Pilar Trelles-Thorne, M., Halpern, D., Frank, Y., Lozano, R., Layton, C., Britvan, B., Bernstein, J. A., Buxbaum, J. D., Berry-Kravis, E., Powell, C. M., Srivastava, S., Sahin, M., Soorya, L., Thurm, A., Kolevzon, A., & Developmental Synaptopathies Consortium. (2022). Strong evidence for genotype-phenotype correlations in Phelan-McDermid syndrome: Results from the developmental Synaptopathies consortium. *Human Molecular Genetics*, *31*, 625–637.

Lutz, A.-K., Pfaender, S., Incearap, B., Ioannidis, V., Ottonelli, I., Föhr, K. J., Cammerer, J., Zoller, M., Higelin, J., Giona, F., Stetter, M., Stoecker, N., Alami, N. O., Schön, M., Orth, M., Liebau, S., Barbi, G., Grabrucker, A. M., Delorme, R., … Boeckers, T. M. (2020). Autism-associated SHANK3 mutations impair maturation of neuromuscular junctions and striated muscles. *Science Translational Medicine*, *12*, eaaz3267.

Lyons-Warren, A. M., Cheung, S. W., & Holder, J. L. (2017). Clinical reasoning: A common cause for Phelan-McDermid syndrome and neurofibromatosis type 2: One ring to bind them. *Neurology*, *89*, e205–e209.

Maltese, P. E., Michelini, S., Ricci, M., Maitz, S., Fiorentino, A., Serrani, R., Lazzerotti, A., Bruson, A., Paolacci, S., Benedetti, S., & Bertelli, M. (2019). Increasing evidence of hereditary lymphedema caused by CELSR1 loss-of-function variants. *American Journal of Medical Genetics. Part A*, *179*, 1718–1724.

McGreevy, P., Fry, T., & Cornwall, C. (2014). *Essential for living: A communication, behavior, and functional skills curriculum, assessment, and professional practitioners handbook*. McGreevy.

Meites, E., Szilagyi, P. G., Chesson, H. W., Unger, E. R., Romero, J. R., & Markowitz, L. E. (2019). Human papillomavirus vaccination for adults: Updated recommendations of the advisory committee on immunization practices. *MMWR. Morbidity and Mortality Weekly Report*, *68*, 698–702.

Messias, E., Kaley, S. N., & McKelvey, K. D. (2013). Adult-onset psychosis and clinical genetics: A case of Phelan-McDermid syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *25*, E27.

Mieses, A. M., Tavassoli, T., Li, E., Soorya, L., Lurie, S., Wang, A. T., Siper, P. M., & Kolevzon, A. (2016). Brief report: Sensory reactivity in children with Phelan-McDermid syndrome. *Journal of Autism and Developmental Disorders*, *46*, 2508–2513.

Mingbunjerdsuk, D., Wong, M., Bozarth, X., & Sun, A. (2021). Co-occurrence of metachromatic leukodystrophy in Phelan-McDermid syndrome. *Journal of Child Neurology*, *36*, 148–151.

Moessner, R., Marshall, C. R., Sutcliffe, J. S., Skaug, J., Pinto, D., Vincent, J., Zwaigenbaum, L., Fernandez, B., Roberts, W., Szatmari, P., & Scherer, S. W. (2007). Contribution of SHANK3 mutations to autism Spectrum disorder. *American Journal of Human Genetics*, *81*, 1289–1297.

Moffitt, B. A., Sarasua, S. M., Ward, L., Ivankovic, D., Valentine, K., Rogers, C., Phelan, K., & Boccuto, L. (2022). Sleep and Phelan-McDermid syndrome: Lessons from the international registry and the scientific literature. *Molecular Genetics & Genomic Medicine*, *10*, e2035.

Naisbitt, S., Kim, E., Tu, J. C., Xiao, B., Sala, C., Valtschanoff, J., Weinberg, R. J., Worley, P. F., & Sheng, M. (1999). Shank, a novel family of postsynaptic density proteins that binds to the NMDA receptor/PSD-95/GKAP complex and cortactin. *Neuron*, *23*, 569–582.

Nemirovsky, S. I., Córdoba, M., Zaiat, J. J., Completa, S. P., Vega, P. A., González-Morón, D., Medina, N. M., Fabbro, M., Romero, S., Brun, B., Revale, S., Ogara, M. F., Pecci, A., Marti, M., Vazquez, M., Turjanski, A., & Kauffman, M. A. (2015). Whole genome sequencing reveals a de novo SHANK3 mutation in familial autism spectrum disorder. *PLoS One*, *10*, e0116358.

Nesslinger, N. J., Gorski, J. L., Kurczynski, T. W., Shapira, S. K., Siegel-Bartelt, J., Dumanski, J. P., Cullen, R. F., French, B. N., & McDermid, H. E. (1994). Clinical, cytogenetic, and molecular characterization of seven patients with deletions of chromosome 22q13.3. *American Journal of Human Genetics*, *54*, 464–472.

Nevado, J., García-Miñaúr, S., Palomares-Bralo, M., Vallespín, E., Guillén-Navarro, E., Rosell, J., Bel-Fenellós, C., Mori, M. Á., Milá, M., Del Campo, M., Barrúz, P., Santos-Simarro, F., Obregón, G., Orellana, C., Pachajoa, H., Tenorio, J. A., Galán, E., Cigudosa, J. C., Moresco, A., … Spanish PMS Working Group. (2022). Variability in Phelan-McDermid syndrome in a cohort of 210 individuals. *Frontiers in Genetics*, *13*, 652454.

Norwood, K. W., Slayton, R. L., & Council on Children With Disabilities, Section on Oral Health. (2013). Oral health care for children with developmental disabilities. *Pediatrics*, *131*, 614–619.

O'Roak, B. J., Stessman, H. A., Boyle, E. A., Witherspoon, K. T., Martin, B., Lee, C., Vives, L., Baker, C., Hiatt, J. B., Nickerson, D. A., Bernier, R., Shendure, J., & Eichler, E. E. (2014). Recurrent de novo mutations implicate novel genes underlying simplex autism risk. *Nature Communications*, *5*, 5595.

Pasini, A., D'Agati, E., Casarelli, L., & Curatolo, P. (2010). Dose-dependent effect of risperidone treatment in a case of 22q13.3 deletion syndrome. *Brain Development*, *32*, 425–427.

Pfaender, S., Sauer, A. K., Hagmeyer, S., Mangus, K., Linta, L., Liebau, S., Bockmann, J., Huguet, G., Bourgeron, T., Boeckers, T. M., & Grabrucker, A. M. (2017). Zinc deficiency and low enterocyte zinc transporter expression in human patients with autism related mutations in SHANK3. *Scientific Reports*, *7*, 45190.

Phelan, K., Boccuto, L., Powell, C. M., Boeckers, T. M., van Ravenswaaij-Arts, C., Rogers, R. C., Sala, C., Verpelli, C., Thurm, A., Bennett, W. E., Winrow, C. J., Garrison, S. R., Toro, R., & Bourgeron, T. (2022). Phelan-McDermid syndrome: A classification system after 30 years of experience. *Orphanet Journal of Rare Diseases*, *17*, 27.

Phelan, K., & McDermid, H. E. (2012). The 22q13.3 deletion syndrome (Phelan-McDermid syndrome). *Molecular Syndromology*, *2*, 186–201.

Phelan, K., Rogers, R. C., & Boccuto, L. (1993). Phelan-McDermid syndrome. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, G. Mirzaa, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle.

Phelan, M. C., Rogers, R. C., Saul, R. A., Stapleton, G. A., Sweet, K., McDermid, H., Shaw, S. R., Claytor, J., Willis, J., & Kelly, D. P. (2001). 22q13 deletion syndrome. *American Journal of Medical Genetics*, *101*, 91–99.

Philippe, A., Boddaert, N., Vaivre-Douret, L., Robel, L., Danon-Boileau, L., Malan, V., de Blois, M.-C., Heron, D., Colleaux, L., Golse, B., Zilbovicius, M., & Munnich, A. (2008). Neurobehavioral profile and brain imaging study of the 22q13.3 deletion syndrome in childhood. *Pediatrics*, *122*, e376–e382.

Ponson, L., Gomot, M., Blanc, R., Barthelemy, C., Roux, S., Munnich, A., Romana, S., Aguillon-Hernandez, N., Malan, V., & Bonnet-Brilhault, F. (2018). 22q13 deletion syndrome: Communication disorder or autism? Evidence from a specific clinical and neurophysiological phenotype. *Translational Psychiatry*, *8*, 146.

Raab, M., Boeckers, T. M., & Neuhuber, W. L. (2010). Proline-rich synapse-associated protein-1 and 2 (ProSAP1/Shank2 and ProSAP2/Shank3)-scaffolding proteins are also present in postsynaptic specializations of the peripheral nervous system. *Neuroscience*, *171*, 421–433.

Ranjitkar, S., Kaidonis, J. A., & Smales, R. J. (2012). Gastroesophageal reflux disease and tooth erosion. *International Journal of Dentistry*, *2012*, 479850.

Reierson, G., Bernstein, J., Froehlich-Santino, W., Urban, A., Purmann, C., Berquist, S., Jordan, J., O'Hara, R., & Hallmayer, J. (2017). Characterizing regression in Phelan McDermid syndrome (22q13 deletion syndrome). *Journal of Psychiatric Research*, *91*, 139–144.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W. W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., & Rehm, H. L. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in Medicine*, *17*, 405–424.

Rollins, J. D., Sarasua, S. M., Phelan, K., DuPont, B. R., Rogers, R. C., & Collins, J. S. (2011). Growth in Phelan-McDermid syndrome. *American Journal of Medical Genetics. Part A*, *155A*, 2324–2326.

Romski, M., Sevcik, R. A., Adamson, L. B., Cheslock, M., Smith, A., Barker, R. M., & Bakeman, R. (2010). Randomized comparison of augmented and nonaugmented language interventions for toddlers with developmental delays and their parents. *Journal of Speech, Language, and Hearing Research*, *53*, 350–364.

Sala, C., Piëch, V., Wilson, N. R., Passafaro, M., Liu, G., & Sheng, M. (2001). Regulation of dendritic spine morphology and synaptic function by Shank and Homer. *Neuron*, *31*, 115–130.

Samogy-Costa, C. I., Varella-Branco, E., Monfardini, F., Ferraz, H., Fock, R. A., Barbosa, R. H. A., Pessoa, A. L. S., Perez, A. B. A., Lourenço, N., Vibranovski, M., Krepischi, A., Rosenberg, C., & Passos-Bueno, M. R. (2019). A Brazilian cohort of individuals with Phelan-McDermid syndrome: Genotype-phenotype correlation and identification of an atypical case. *Journal of Neurodevelopmental Disorders*, *11*, 13.

Sanchez-Larsen, A., Aznar-Lain, G., Benito, B., Principe, A., Ley, M., Tauste Campo, A., & Rocamora, R. (2017). Post-ictal atrial fibrillation detected during video-EEG monitoring: Case report, proposed physiopathologic mechanism and therapeutic considerations. *Epilepsy & Behavior Case Reports*, *8*, 40–43.

Sarasua, S. M., Boccuto, L., Sharp, J. L., Dwivedi, A., Chen, C.-F., Rollins, J. D., Rogers, R. C., Phelan, K., & DuPont, B. R. (2014). Clinical and genomic evaluation of 201 patients with Phelan–McDermid syndrome. *Human Genetics*, *133*, 847–859.

Sarasua, S. M., Dwivedi, A., Boccuto, L., Rollins, J. D., Chen, C.-F., Rogers, R. C., Phelan, K., DuPont, B. R., & Collins, J. S. (2011). Association between deletion size and important phenotypes expands the genomic region of interest in Phelan–McDermid syndrome (22q13 deletion syndrome). *Journal of Medical Genetics*, *48*, 761–766.

Sathyamoorthi, S., Morales, J., Bermudez, J., McBride, L., Luquette, M., McGoey, R., Oates, N., Hales, S., Biegel, J. A., & Lacassie, Y. (2009).

Array analysis and molecular studies of INI1 in an infant with deletion 22q13 (Phelan-McDermid syndrome) and atypical teratoid/rhabdoid tumor. *American Journal of Medical Genetics. Part A*, *149A*, 1067–1069.

Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M. S., De Rubeis, S., An, J.-Y., Peng, M., Collins, R., Grove, J., Klei, L., Stevens, C., Reichert, J., Mulhern, M. S., Artomov, M., Gerges, S., Sheppard, B., Xu, X., Bhaduri, A., Norman, U., … Buxbaum, J. D. (2020). Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. *Cell*, *180*, 568–584.e23.

Schenkel, L. C., Aref-Eshghi, E., Rooney, K., Kerkhof, J., Levy, M. A., McConkey, H., Rogers, R. C., Phelan, K., Sarasua, S. M., Jain, L., Pauly, R., Boccuto, L., DuPont, B., Cappuccio, G., Brunetti-Pierri, N., Schwartz, C. E., & Sadikovic, B. (2021). DNA methylation epi-signature is associated with two molecularly and phenotypically distinct clinical subtypes of Phelan-McDermid syndrome. *Clinical Epigenetics*, *13*, 2.

Serrada-Tejeda, S., Cuadrado, M.-L., Martínez-Piédrola, R. M., Máximo-Bocanegra, N., Sánchez-Herrera-Baeza, P., Camacho-Montaño, L. R., & Pérez-de-Heredia-Torres, M. (2022). Sensory processing and adaptive behavior in Phelan-McDermid syndrome: A cross-sectional study. *European Journal of Pediatrics*, *181*, 3141–3152.

Serret, S., Thümmler, S., Dor, E., Vesperini, S., Santos, A., & Askenazy, F. (2015). Lithium as a rescue therapy for regression and catatonia features in two SHANK3 patients with autism spectrum disorder: Case reports. *BMC Psychiatry*, *15*, 107.

Severio, A., Monagas, J., Noel, R. A., & Hyman, P. E. (2015). Eliminating rumination in developmentally disabled children: A case report. *Pediatrics*, *136*, e249–e251.

Slifer, K. J., Avis, K. T., & Frutchey, R. A. (2008). Behavioral intervention to increase compliance with electroencephalographic procedures in children with developmental disabilities. *Epilepsy & Behavior*, *13*, 189–195.

Smith-Hicks, C., Wright, D., Kenny, A., Stowe, R. C., McCormack, M., Stanfield, A. C., & Holder, J. L. (2021). Sleep abnormalities in the Synaptopathies-SYNGAP1-related intellectual disability and Phelan-McDermid syndrome. *Brain Sciences*, *11*, 1229.

Soorya, L., Kolevzon, A., Zweifach, J., Lim, T., Dobry, Y., Schwartz, L., Frank, Y., Wang, A. T., Cai, G., Parkhomenko, E., Halpern, D., Grodberg, D., Angarita, B., Willner, J. P., Yang, A., Canitano, R., Chaplin, W., Betancur, C., & Buxbaum, J. D. (2013). Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. *Molecular Autism*, *4*, 18.

Soorya, L., Leon, J., Trelles, M. P., & Thurm, A. (2018). Framework for assessing individuals with rare genetic disorders associated with profound intellectual and multiple disabilities (PIMD): The example of Phelan McDermid syndrome. *The Clinical Neuropsychologist*, *32*, 1226–1255.

Srikanth, S., Jain, L., Zepeda-Mendoza, C., Cascio, L., Jones, K., Pauly, R., DuPont, B., Rogers, C., Sarasua, S., Phelan, K., Morton, C., & Boccuto, L. (2021). Position effects of 22q13 rearrangements on candidate genes in Phelan-McDermid syndrome. *PLoS One*, *16*, e0253859.

Srivastava, S., Condy, E., Carmody, E., Filip-Dhima, R., Kapur, K., Bernstein, J. A., Berry-Kravis, E., Powell, C. M., Soorya, L., Thurm, A., Buxbaum, J. D., Sahin, M., Kolevzon, A. L., & Developmental Synaptopathies Consortium. (2021). Parent-reported measure of repetitive behavior in Phelan-McDermid syndrome. *Journal of Neurodevelopmental Disorders*, *13*, 53.

Srivastava, S., Scherrer, B., Prohl, A. K., Filip-Dhima, R., Kapur, K., Kolevzon, A., Buxbaum, J. D., Berry-Kravis, E., Soorya, L., Thurm, A., Powell, C. M., Bernstein, J. A., Warfield, S. K., Sahin, M., & Developmental Synaptopathies Consortium. (2019). Volumetric analysis of the basal ganglia and cerebellar structures in patients with Phelan-McDermid syndrome. *Pediatric Neurology*, *90*, 37–43.

Tabet, A.-C., Rolland, T., Ducloy, M., Lévy, J., Buratti, J., Mathieu, A., Haye, D., Perrin, L., Dupont, C., Passemard, S., Capri, Y., Verloes, A., Drunat, S., Keren, B., Mignot, C., Marey, I., Jacquette, A., Whalen, S., Pipiras, E., … Bourgeron, T. (2017a). A framework to identify contributing genes in patients with Phelan-McDermid syndrome. *NPJ Genomic Medicine*, *2*, 32.

Tabet, A.-C., Rolland, T., Ducloy, M., Lévy, J., Buratti, J., Mathieu, A., Haye, D., Perrin, L., Dupont, C., Passemard, S., Capri, Y., Verloes, A., Drunat, S., Keren, B., Mignot, C., Marey, I., Jacquette, A., Whalen, S., Pipiras, E., … Bourgeron, T. (2017b). A framework to identify contributing genes in patients with Phelan-McDermid syndrome. Npj. *Genomic Medicine*, *2*, 1–9.

Tavassoli, T., Layton, C., Levy, T., Rowe, M., George-Jones, J., Zweifach, J., Lurie, S., Buxbaum, J. D., Kolevzon, A., & Siper, P. M. (2021). Sensory reactivity phenotype in Phelan-McDermid syndrome is distinct from idiopathic ASD. *Genes (Basel)*, *12*, 977.

Torti, E., Keren, B., Palmer, E. E., Zhu, Z., Afenjar, A., Anderson, I. J., Andrews, M. V., Atkinson, C., Au, M., Berry, S. A., Bowling, K. M., Boyle, J., Buratti, J., Cathey, S. S., Charles, P., Cogne, B., Courtin, T., Escobar, L. F., Finley, S. L., … Juusola, J. (2019). Variants in TCF20 in neurodevelopmental disability: Description of 27 new patients and review of literature. *Genetics in Medicine*, *21*, 2036–2042.

Tufano, M., Della Corte, C., Cirillo, F., Spagnuolo, M. I., Candusso, M., Melis, D., Torre, G., & Iorio, R. (2009). Fulminant autoimmune hepatitis in a girl with 22q13 deletion syndrome: A previously unreported association. *European Journal of Pediatrics*, *168*, 225–227.

U.S. Department of Health and Human Service, Health Resources and Service Administration, Maternal and Child Health Bureau. (2013). *The National Survey of children with special health care needs chartbook 2009–2010*. U.S. Department of Health and Human Services.

Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., Verhulst, F., Luijk, M. P. C. M., & Tiemeier, H. (2018). The bidirectional association between sleep problems and autism spectrum disorder: A population-based cohort study. *Molecular Autism*, *9*, 8.

Verhoeven, W. M. A., Egger, J. I. M., & de Leeuw, N. (2020). A longitudinal perspective on the pharmacotherapy of 24 adult patients with Phelan McDermid syndrome. *European Journal of Medical Genetics*, *63*, 103751.

von Gontard, A. (2013). Urinary incontinence in children with special needs. *Nature Reviews. Urology*, *10*, 667–674.

von Gontard, A., Pirrung, M., Niemczyk, J., & Equit, M. (2015). Incontinence in children with autism spectrum disorder. *Journal of Pediatric Urology*, *11*, 264.e1–264.e7.

Williams Buckley, A., Hirtz, D., Oskoui, M., Armstrong, M. J., Batra, A., Bridgemohan, C., Coury, D., Dawson, G., Donley, D., Findling, R. L., Gaughan, T., Gloss, D., Gronseth, G., Kessler, R., Merillat, S., Michelson, D., Owens, J., Pringsheim, T., Sikich, L., … Ashwal, S. (2020). Practice guideline: Treatment for insomnia and disrupted sleep behavior in children and adolescents with autism spectrum disorder: Report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology. *Neurology*, *94*, 392–404.

Wilson, H. L., Wong, A. C. C., Shaw, S. R., Tse, W.-Y., Stapleton, G. A., Phelan, M. C., Hu, S., Marshall, J., & McDermid, H. E. (2003). Molecular characterisation of the 22q13 deletion syndrome supports the role of haploinsufficiency of SHANK3/PROSAP2 in the major neurological symptoms. *Journal of Medical Genetics*, *40*, 575–584.

Witmer, C., Mattingly, A., D'Souza, P., Thurm, A., & Hadigan, C. (2019). Incontinence in Phelan-McDermid syndrome. *Journal of Pediatric Gastroenterology and Nutrition*, *69*, e39–e42.

Xu, N., Lv, H., Yang, T., Du, X., Sun, Y., Xiao, B., Fan, Y., Luo, X., Zhan, Y., Wang, L., Li, F., & Yu, Y. (2020). A 29 mainland Chinese cohort of patients with Phelan-McDermid syndrome: Genotype-phenotype correlations and the role of SHANK3 haploinsufficiency in the important phenotypes. *Orphanet Journal of Rare Diseases*, *15*, 335.

Yuen, R. K. C., Merico, D., Bookman, M., Howe, J., Thiruvahindrapuram, B., Patel, R. V., Whitney, J., Deflaux, N., Bingham, J., Wang, Z.,

Pellecchia, G., Buchanan, J. A., Walker, S., Marshall, C. R., Uddin, M., Zarrei, M., Deneault, E., D'Abate, L., Chan, A. J. S., … Scherer, S. W. (2017). Whole genome sequencing resource identifies 18 new candidate genes for autism spectrum disorder. *Nature Neuroscience*, *20*, 602–611.

Ziats, C. A., Jain, L., McLarney, B., Vandenboom, E., DuPont, B. R., Rogers, C., Sarasua, S., Nevado, J., Cordisco, E. L., Phelan, K., & Boccuto, L. (2020). Neurofibromatosis type 2 in Phelan-McDermid syndrome: Institutional experience and review of the literature. *European Journal of Medical Genetics*, *63*, 104042.

Zwanenburg, R. J., Bocca, G., Ruiter, S. A. J., Dillingh, J. H., Flapper, B. C. T., van den Heuvel, E. R., & van Ravenswaaij-Arts, C. M. A. (2016). Is there an effect of intranasal insulin on development and behaviour in Phelan-McDermid syndrome? A randomized, double-blind, placebo-controlled trial. *European Journal of Human Genetics*, *24*, 1696–1701.

Zwanenburg, R. J., Ruiter, S. A. J., van den Heuvel, E. R., Flapper, B. C. T., & Van Ravenswaaij-Arts, C. M. A. (2016). Developmental phenotype in Phelan-McDermid (22q13.3 deletion) syndrome: A systematic and prospective study in 34 children. *Journal of Neurodevelopmental Disorders*, *8*, 16.

How to cite this article: Srivastava, S., Sahin, M., Buxbaum, J. D., Berry-Kravis, E., Soorya, L. V., Thurm, A., Bernstein, J. A., Asante-Otoo, A., Bennett, W. E. Jr, Betancur, C., Brickhouse, T. H., Passos Bueno, M. R., Chopra, M., Christensen, C. K., Cully, J. L., Dies, K., Friedman, K., Gummere, B., Holder, J. L. Jr, … Kolevzon, A. (2023). Updated consensus guidelines on the management of Phelan–McDermid syndrome. *American Journal of Medical Genetics Part A*, *191*A:2015–2044. https://doi.org/10.1002/ajmg.a.63312