Autism Spectrum Disorder Associated with Germline Heterozygous $PTEN$ Mutations

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This review examines our current understanding of autism spectrum disorder (ASD), its prevalence, impact, behavioral treatment, and outcomes. Building on this knowledge, ASD associated with $PTEN$ mutations is introduced and recent human studies of neurobehavioral and neuroimaging findings in patients with $PTEN$ mutations with and without ASD are reviewed. In doing so, we present evidence supporting a model of $PTEN$ loss leading to neurobehavioral deficits, including ASD and intellectual disability. Next, we describe the neurobehavioral spectrum observed across $PTEN$ mutation cases, adding specificity where possible, based on data from recent studies of child and adult $PTEN$ patients. Finally, we end with a discussion of potential clinical recommendations for improving interventions and supports for people with $PTEN$-ASD and future research avenues for understanding and treating the functional and cognitive deficits in $PTEN$-ASD.

Autism spectrum disorder (ASD) represents a diverse set of neurodevelopmental conditions with a wide range of behavioral manifestations (Levy et al. 2009; Muhle et al. 2018). Two symptom dimensions, deficits in social communication/interaction (SCI) and the presence of restricted/repetitive behaviors (RRBs), are the core features of the disorder (American Psychiatric Association 2013). The ASD diagnosis has high interrater reliability (van Daalen et al. 2009; Lord et al. 2012) and temporal stability (Lord et al. 2006; Chawarska et al. 2009; van Daalen et al. 2009), with only a small percentage of cases identified in early childhood no longer meeting diagnostic criteria in later childhood, adolescence, or adulthood (Billstedt et al. 2005; Fein et al. 2013). Yet, individual behavioral presentations are highly variable (Eaves and Ho 2008) and largely driven by cognitive level, which can range from severely impaired to very superior ability. Across cognitive levels, significant decreases in social function and quality of life are common (Barneveld et al. 2014) and even the most capable individuals often show problems navigating complex social interactions. Intellectual disability (ID) is present in ~30% of ASD cases (Baio et al. 2018), further complicating presentation and driving functional impairment, and co-occurring medical and mental health conditions are common, including seizure disorder, gastrointestinal (GI) problems, attention-deficit/hyperactivity disorder (ADHD), anxiety, and other conditions (Fig. 1; Bauman 2010; Rosen et al. 2018). Some estimates indicate as many as 90% of individuals with autism have at least one co-occurring medical or mental
health condition (Simonoff et al. 2008; Salazar et al. 2015; Mazurek and Sohl 2016), including at least 25% with severe behavioral disturbance (Lecavalier 2006).

Updated Centers for Disease Control and Prevention (CDC) prevalence estimates indicate 1 in 59 (1 in 36 boys) 8-year-old children meet ASD criteria (Baio et al. 2018), and recent CDC (Christensen et al. 2019) and direct prevalence estimates (Kim et al. 2011) suggest these numbers are conservative. This represents a massive increase in the prevalence of autism over the past three decades. The increase is, at least in part, a result of increased awareness and recommended screening at 18 and 24 months (Miller et al. 2011; Muhle et al. 2018), although diagnostic accretion/substitution (Shattuck 2006a,b; Weintraub 2011) and other risk factors such as advanced parental age (Hultman et al. 2011; Sandin et al. 2012; Wu et al. 2017) and prematurity (Agrawal et al. 2018) appear to be contributing. Because of increased prevalence and substantial functional disability associated with autism, incremental individual, and society costs are substantial. Lifetime costs per individual have been estimated at 1.4 million dollars for ASD without ID and 2.4 million for ASD with ID (Buescher et al. 2014). The annual impact to the U.S. economy in 2015 was estimated to be at least 268 billion dollars (Leigh and Du 2015), with most of the incremental costs occurring in adulthood (Buescher et al. 2014). Many adults with autism, even those with greater functional capacity, have very poor postsecondary education and employment outcomes, including more than 50% of young adults who had no participation in postsecondary education or employment 2 years after high school (Shattuck et al. 2012). Thus, ASD has become a major public health challenge.

Thankfully, many of the identification, intervention, and outcome data points are trending in a positive direction. Early identification is improving: the average age of diagnosis in the United States is now ~4 years old (Baio et al. 2018; Christensen et al. 2019), a substantial reduction over a decade ago (Shattuck et al. 2009).
Additional improvements in early identification are needed though, because many early autism signs can be reliably detected by 12 months (Pierce et al. 2011; Samango-Sprouse et al. 2015; Miller et al. 2017) and potentially 50% of autism cases can be identified before 15 months. Identifying children early is important for maximizing the effectiveness of interventions. Early intensive behaviorally based interventions have been shown to be effective for many children (Eldevik et al. 2009; Howlin et al. 2009; Dawson et al. 2010; Rogers et al. 2019). Recent data suggest that age at intervention start improves outcomes (Smith et al. 2015), although the magnitude of benefit varies across children (Howlin et al. 2009; Warren et al. 2011) and adult outcomes are highly variable (Howlin et al. 2004; Anderson et al. 2014; Howlin and Magiati 2017).

**AUTISM AND GENETICS**

Because of substantial variability in the outcome of early intensive interventions, the urgency to discover underlying pathophysiology and identify effective personalized medicine treatments has never been greater. This task has proved a major challenge as autism is an etiologically heterogeneous condition with a strong but complex genetic component (Geschwind 2009; Muhle et al. 2018). Twin studies have estimated ASD heritability to be 50%–90%+ (Ronald and Hoekstra 2011; Tick et al. 2016) and recurrence risk in siblings is substantial (~20%) (Ozonoff et al. 2011). However, only ~20% of cases have a known genetic etiology, identified primarily through relationships with genetic syndromes (Abrahams and Geschwind 2008), copy number variation (Sebat et al. 2007; Levy et al. 2011; Sanders et al. 2011), and small-scale gene-disrupting variants (O’Roak et al. 2011; Schaaf et al. 2011; Sanders et al. 2012). Recent large-scale sequencing studies have identified likely causative de novo variants within more than 60 genes (Yuen et al. 2017). The residual ~80% of ASD remains “idiopathic” (Abrahams and Geschwind 2008). As a result, the vast majority of studies of ASD pathophysiology have been conducted on idiopathic ASD. Unfortunately, but not surprisingly, attempts at identifying molecular and cellular pathophysiology in these samples have been hampered by massive phenotypic and genetic heterogeneity. One approach to identifying pathophysiology and mechanism-based treatments for ASD is to focus on subgroups of cases with a recognized genetic etiology.

**PTEN AND ASD**

Macrocephaly is a well-known phenotype within idiopathic ASD cases (Lainhart et al. 2006). Estimates suggest that ~15% of ASD cases have macrocephaly defined as >2 SDs per age norms (Sacco et al. 2015). Early life acceleration in brain growth is a likely mechanism (Hazlett et al. 2017) and this appears to extend beyond cases with macrocephaly, as there is a general shift in the head circumference distribution in ASD (Lainhart 2003, 2006). A growing body of literature has implied a relationship between the tumor suppressor gene, PTEN, and ASD with macrocephaly (Butler et al. 2005; Yehia et al. 2019). Initial cases were suggestive of an association (Delatycki et al. 2003; Eng 2003) and subsequent small cohort studies identified an enriched number of PTEN mutations in ASD cases with macrocephaly (PTEN-ASD) (Butler et al. 2005; Buxbaum et al. 2007). Later cohorts with larger samples of individuals with ASD and/or ID (neurodevelopmental delay) found similar proportions of PTEN mutations (Herman et al. 2007; Orrico et al. 2009; Varga et al. 2009; McBride et al. 2010; Hobert et al. 2014), resulting in a weighted average of 17% of macrocephalic ASD and translating to approximately 2% of all ASD cases (Tilot et al. 2015). Approaching ASD prevalence from the PTEN mutation angle, recent case series have suggested that 25%–50% of children with PTEN mutations are identified with ASD (Hansen-Kiss et al. 2017; Ciaccio et al. 2018). Taken together, these studies clearly established a link between PTEN mutations and ASD with or without ID and suggested a wide behavioral spectrum, from severe cognitive and functional disability to intact cognition and daily living skills. Yet, PTEN-ASD as a subset of idiopathic ASD has only recently been studied in detail.
PTEN-ASD NEUROBEHAVIORAL FINDINGS

In 2015, we published the first comprehensive phenotypic characterization of a small cohort (n = 17) of PTEN-ASD cases (ages 2–25) and compared them to demographically comparable patients with idiopathic macrocephalic ASD (n = 16), idiopathic normocephalic ASD (n = 38), and healthy controls (n = 14) (Frazier et al. 2015). This study confirmed wide variability in clinical presentation but also identified several interesting group trends and differences. Not surprisingly, the PTEN-ASD group had a significantly larger head circumference (mean z = 4.2) than even the macro-ASD group (mean z = 2.9). Intriguingly, PTEN-ASD showed no significant differences in clinician-rated autism symptom domains or parent-reported autism traits but showed substantially lower IQ (global, verbal, and nonverbal), slower processing speed, and reduced working memory (Fig. 2). Sustained attention and auditory and visual long-term memory were also reduced but the effect was not as strong as for other cognitive measures. Adaptive function was also weaker in PTEN-ASD with a particularly strong impact on motor skills and community living skills. Using remote eye gaze tracking, social attention deficits were identified that were highly similar to idiopathic autism cases. Subsequent analysis of data from this cohort also found that PTEN-ASD shows less emotion dysregulation than other ASD groups (unpubl.). The finding of less emotion dysregulation is consistent with clinical observations of PTEN-ASD children being generally happy and passive and showing less emotional lability around changes in environment and routine, a distinct difference from idiopathic ASD.

PTEN-ASD MOLECULAR FINDINGS AND BRAIN PATHOLOGY

Molecular data from Frazier et al. (2015) identified significant reductions in PTEN protein levels in PTEN-ASD relative to other groups (Fig. 3A), but there were no obvious changes in other plasma-derived protein levels. Magnetic resonance imaging (MRI) data, obtained on a subset of patients, revealed increased global white matter volume (cm³) (Fig. 3A), corpus callosum volume, and white matter hypointensities. The latter were observable on T1 images and tended to cluster in periventricular regions (Fig. 3C). Cross-level structural mediational model results indicated that PTEN protein loss was a strong driver of white matter abnormalities, which, in turn, led to reduced global cognitive ability (Fig. 4). This model represents the first attempt to understand cross-level molecu-
lar, neural systems, and neurobehavioral findings in PTEN-ASD and suggests that white matter abnormalities may be a biomarker for neurobehavioral deficits. The potential of MRI-measured white matter abnormalities to be a treatment target for fast-fail clinical trials is intriguing, as this may allow for more rapid evaluation of compounds influencing PTEN-related pathways in future studies.

The prominent white matter pathology in human PTEN-ASD is consistent with white matter findings in mouse models of Pten loss (reviewed in detail in Page 2019), including gene expression in mouse cortex from a cytoplasmic predominant mouse model and myelin sheath unraveling in conditional Pten knockout models (Fraser et al. 2004, 2015; Tilot et al. 2014). Overall, this pattern of early developmental abnormalities in white matter is suggestive of AKT pathway dysregulation as a plausible molecular mechanism for PTEN loss leading to enhanced but abnormal brain myelination (Zhou et al. 2003; Flores et al. 2008). Additionally, the observation of several ASD-related genetic syndromes impacting PI3K/AKT pathway activation suggests that this may be one of the primary molecular pathways contributing to ASD associated with early abnormal brain growth. In the case of PTEN loss, it is plausible that AKT activation disrupts functional connectivity through abnormal myelination and via neuronal hypertrophy with increased dendritic branching (Fraser et al. 2004; Kwon et al. 2006). Figure 5 depicts a cross-level model of Pten loss leading to neurobehavioral dysfunction. In this model, Pten loss results in abnormal brain connectivity, which gives rise to cognitive deficits that preferentially impact frontal–subcortical functions such as working memory, processing speed, and fine/gross motor skills. The lower levels of the model are based, in part, on larger effect sizes for those measures in our patient characterization study and the fact that accounting for processing speed, working memory, and motor difficulties appears to account for most of the full-scale IQ reductions. The model also depicts links between abnormal connectivity and impairments in social attention, perseveration, and language/communication, key frontal lobe–mediated functions that underlie autism symptoms.

Figure 3. Molecular and white matter findings from data in Frazier et al. (2015), including (A) PTEN protein level, (B) total brain white matter, and (C) white matter hypointensities depicted on T1 using magnetic resonance imaging (MRIs). ASD, Autism spectrum disorder.
White matter abnormalities have also been identified in MRI studies of patients with PTEN mutations without ASD (Vanderver et al. 2014). MRI investigations of the broader PTEN population have also found vascular anomalies (Lok et al. 2005; Ciaccio et al. 2018), enlarged periventricular spaces (Vanderver et al. 2014; Ciaccio et al. 2018), cerebellar overgrowth/Lhermitte–Duclos (Lok et al. 2005), cortical dysplasia (Adachi et al. 2018), and Chiari 1 malformation (Salletti et al. 2017; Ciaccio et al. 2018). It remains unclear whether the exact pattern of MRI abnormalities will differ when ASD, ID, or other neurodevelopmental disorders are present as part of the phenotypic picture. It is also uncertain whether the magnitude of white matter pathology, which appears to be prevalent across the PTEN population, will be substantively greater in patients with ASD and/or ID. These will be fruitful areas for future investigation.

**PTEN NEUROBEHAVIORAL SPECTRUM**

Irrespective of the exact pattern of neuropathology across PTEN cases, the PTEN-ASD neurobehavioral phenotype appears to be a more extreme presentation of the frontal–subcortical dysfunction observed in adults with PTEN mutations without ASD (Busch et al. 2013). Busch et al. (2013) completed a comprehensive neurobehavioral evaluation of 5 children and 20 adults with PTEN hamartoma tumor syndrome (PHTS). The study found a wide variance in general cognitive ability and mild but detectable reductions in executive functioning and fine motor dexterity. The pattern further supports the picture of a wide phenotypic spectrum for PTEN cases, from no cognitive or neuropsychiatric impairment to a substantively impaired cognitive and neuropsychiatric presentation.

Figure 6 presents the observed cognitive and neuropsychiatric spectrum in PTEN mutation cases. The findings of Busch et al. (2013) provide specificity to the top two levels of Figure 6, while Frazier et al. (2015) characterized individuals with ASD at the bottom three levels. In this model, individuals with mild features show relative deficits in high-level frontal functions such as planning, organizing, and working memory. At the moderate level, developmental history reveals more obvious delays and more substantial frontal–subcortical dysfunction, including problems with initiating, processing speed, and fine motor skills. At the severe level, a developmental history reveals global developmental delays and very significant frontal–subcortical and temporal–parietal dysfunction leading to reduced global cognitive ability and substantial difficulties with language and communication. Many of these individuals will be nonverbal or minimally verbal, requiring alternative, augmentative communication. Ongoing multisite studies are underway to further clarify the cognitive and neuropsychiatric spectrum hypothesis, including comparison of PTEN-ASD to PTEN without ASD cases. These studies will be crucial for identifying future neurocognitive treatment targets for clinical trials and for clarifying the best methods for building on cognitive strengths and accommodating or addressing cognitive weakness to maximize adaptive function.
Figure 5. Hypothesized cross-level model linking PTEN loss to autism spectrum disorder (ASD) and neurobehavioral deficits. In this model, PTEN mutations result in PTEN protein reductions, AKT pathway activation, abnormal brain connectivity preferentially affecting frontal–subcortical circuits, and, ultimately, cognitive and motor impairments characteristic of autism and intellectual disability. Boxes from the top down denote targeted sequencing of macrocephalic developmental disability cohorts, and whole-exome sequencing of idiopathic ASD cases support associations between PTEN mutations and ASD/intellectual disability (ID) (Goffin et al. 2001; Butler et al. 2005; Buxbaum et al. 2007; Herman et al. 2007; Orrico et al. 2009; McBride et al. 2010; O’Roak et al. 2014). PTEN mutations result in lower PTEN/Pten protein levels in human ASD cases (Frazier et al. 2015) and a Pten mouse model (Tilot et al. 2014). Multiple publications report associations between PTEN/Pten loss and AKT/Akt activation (Cantley and Neel 1999; Weng et al. 2001; Zhou et al. 2003). Flores et al. (2008) connected Akt overexpression to enhanced myelination. Pten mouse models demonstrate increased myelination with abnormal myelin sheath wrapping (Fraser et al. 2004). Human studies using magnetic resonance imaging (MRI) support abnormal white matter development (Lok et al. 2005; Orrico et al. 2009; Vanderver et al. 2014; Frazier et al. 2015). Multiple publications identify hypertrophic neurons with increased dendritic branching in Pten mouse models (Kwon et al. 2001, 2006; Fraser et al. 2004; Amiri et al. 2012). Although direct links to aberrant functional connectivity have not been established in human PTEN cases, PTEN-related pathway involvement strongly suggests the development of abnormal neural connectivity (van Diepen and Eickholt 2008; Huang et al. 2016). Altered functional connectivity has been established in idiopathic ASD cases (O’Reilly et al. 2017). Distance underconnectivity is associated with autism symptom severity (Yerys et al. 2017), with the primary disruptions in frontal networks (Just et al. 2007; Mostofsky et al. 2009). Abnormal functional connectivity is likely to have a disproportionate effect on the development and functional capacity of frontal–subcortical circuits. Frontal–subcortical dysfunction in PTEN-ASD is supported by neurobehavioral findings in both children (Frazier et al. 2015) and adults (Busch et al. 2013). Altered social attention was recently identified (unpubl.) in our most recent cohort of PTEN mutation carriers with ASD. Multiple forms of perseveration, including repetitive motor mannerisms and restricted interests, have been clinically identified in PTEN-ASD cases (Frazier et al. 2015). Although not ubiquitous, decreased receptive and expressive language test scores are observed as a prominent characteristic of many PTEN-ASD cases (Frazier et al. 2015). Motor dysfunction has been observed in the early developmental course of nearly all PTEN-ASD cases identified to date (Frazier et al. 2015). Reduced working memory and processing speed have been found in two cohorts of PTEN-ASD cases and these deficits have been shown to at least partially mediate IQ reductions (Frazier et al. 2015). Alternative mechanisms not included in the figure are MAPK/ERK pathway activation (Chung et al. 2006), mitochondrial disruptions (Liang et al. 2014; Das Banerjee et al. 2017), neuroinflammation (Tilot et al. 2016), and alterations in monoamine neurotransmitters (Page et al. 2009; He et al. 2015). Also, not included in the model is the observation that PTEN loss may result in cortical dysplasia that precipitates seizures (Elia et al. 2012; Child and Cascino 2013).
CLINICAL RECOMMENDATIONS FOR PTEN-ASD EVALUATION AND INTERVENTION

Existing data indicate that many PTEN cases showing functional deficits, particularly those with ASD and/or ID, should receive a comprehensive neurobehavioral evaluation in addition to recommended PHTS medical evaluation and surveillance. A paired-down version of this evaluation could be conducted as early as ages 3–4 to identify early intervention targets and, by ages 5–7, a fuller evaluation can be conducted to guide education and treatment and inform the team of the individual’s cognitive strengths and weaknesses. Ideally, the multidisciplinary evaluation team will include a psychologist, physician (developmental pediatrician, neurologist, or pediatric psychiatrist if significant behavioral issues are present), and a speech/language pathologist. Using our neurobehavioral findings for PTEN-ASD as a guide, the evaluation battery should include an efficient indicator of global ability with verbal and nonverbal components, measures of sustained attention, working memory, and processing speed, receptive and expressive language, and, for older/cognitively able children, pragmatic language skills. The evaluation should collect data on fine and gross motor skills, adaptive function, autism symptoms (preferably by parent report and clinician observation), and other behavioral symptoms. A small minority of children with PTEN-ASD have had concerning challenging behavior (including pica, elopement, aggression, and self-injury) and a larger minority evaluated to date have been nonverbal or minimally verbal with substantial functional communication needs. In these cases, an evaluation for an augmentative/alternative communication device or a functional behavioral assessment should be considered.

Findings reviewed above suggest prominent working memory and processing speed deficits, as well as sustained attention weaknesses, across the spectrum of PTEN-ASD. For individuals

Figure 6. Observed neurobehavioral (NB) spectrum in PTEN mutation cases.
with this pattern, it is important that educators, therapists, caregivers, and other support personnel take steps to ensure that attention has been gained, speak slowly without infantilizing, use repetition and attention questions to ensure information is encoded and retrievable, and keep directives to a reasonable length (minimize multistep directives). Planning and organizing information is likely to be difficult for many PTEN-ASD individuals and the broader PTEN population, and therefore supports and accommodations will be key. Using visual schedules, planners, timers, and other assistive technology can circumvent problems related to organizational weaknesses. Teaching chains of behaviors using techniques such as forward or backward chaining with reinforcement for completion can allow individuals to experience success in multistep tasks that require organization/planning.

For individuals with significant language and communication challenges, speech/language therapy is essential. Similarly, nearly all individuals with PTEN-ASD seen in our clinics to date have had fine and/or gross motor challenges. Occupational and physical therapy is key and should be sustained even when the difficulties appear to have improved because a variable pattern of improvement and worsening has been observed in some cases. Many individuals with PTEN-ASD show substantial cognitive, functional, and social difficulties that would benefit from early intensive behavioral interventions and, for those with severe challenges, ongoing intensive behavioral intervention may be needed. When engaging with these intensive therapies, it is crucial that initial cognitive and functional evaluations be done to optimize initial therapy targets and programs. Measures such as the Verbal Behavior Milestones Assessment and Placement Program (VB-MAPP) or the Assessment of Basic Language and Learning Skills-Revised (ABLL-R) can be administered to enhance target and program selection.

NEXT STEPS IN PTEN-ASD RESEARCH

Given the relatively limited literature to date on PTEN-ASD, the existing findings merit replication and there are numerous research questions that remain unstudied. An ongoing multisite National Institutes of Health (NIH)-funded natural history study of PTEN-ASD is underway, with the first few years of longitudinal collection completed. Early unpublished results support the above-described pattern of wide variability in cognitive function with prominent frontal–subcortical deficits. It will be important, as this study progresses, that analyses are conducted to confirm and extend information on the published cross-sectional neurobehavioral patterns. As additional waves of longitudinal data are collected, it will be possible to explore average change over time in neurobehavioral measures as well as individual differences in change. If individual differences in neurobehavioral change are found, it may be possible to evaluate predictors of change. If some of these include modifiable factors, including interventions, this information could be used to maximize developmental outcomes in future children with PTEN-ASD. Finally, it will permit exploration of both cross-sectional and longitudinal cross-level relationships between molecular, neural systems, cognitive, and behavioral measures. Cross-level analyses offer the potential to build a comprehensive model of PTEN loss, testing hypothesized relationships from Figure 5, and exploring other molecular contributions to brain abnormalities and neurobehavioral deficits. For example, PTEN classically inhibits MAPK/ERK pathway activation and also has noncanonical associations with metabolic processes (Chen et al. 2018), insulin signaling (Gratuze and Planel 2017), lipid metabolism (Johnson and Stiles 2016), tyrosine hydroxylase (He et al. 2015), dopamine D2 receptors (He et al. 2015), and glycogen regulation (Bai et al. 2017; Song et al. 2018). Because the ongoing multisite study is also collecting data from patients with SHANK3 and TSC1/2 mutations, conditions with high rates of ASD, there is also the potential to compare molecular, neural systems, and neurobehavioral measures across ASD-associated genetic syndromes.

As part of the NIH-funded study, the first-ever pilot clinical trial examining Everolimus as a potential therapeutic for PTEN-ASD is underway. The primary outcome of the trial is a composite neurocognitive frontal function measure.
and the trial uses a 6-month treatment period, which is important for detecting changes in cognition and behavior. Unfortunately, there is no justification yet for repeated MRI in PTEN-ASD. As a result, it is difficult to collect MRI-derived white matter measurements as a key outcome in the trials. This raises the need to identify additional sensitive biomarkers that can be more easily collected and measured repeatedly. Resting and task-focused EEG frequency spectrum and coherence measures may be useful for detecting long-distance connectivity changes that would be expected to be observed with white matter abnormalities (Murias et al. 2007). If these markers can be identified, future clinical trials may adopt a fast-fail approach where target engagement is confirmed and rapid evaluation of brain or biochemical signatures that presage clinical improvement can be included. Future clinical trials of other modifiers of PTEN-related pathways should also be considered in future studies. Expanding the type and targets of investigated compounds could advance the search for efficacy. If multiple useful therapeutics can be identified, this would raise the potential to combine therapeutics to reduce side effects and maximize efficacy.

Additional questions that should be explored in future research include larger cohort evaluations of the prevalence of ASD and/or ID in people with PTEN mutations; differences in specific ASD symptoms when comparing PTEN-ASD to idiopathic cases; responses to behavioral, occupational, and physical therapy interventions; and the prevalence of co-occurring medical and mental health conditions in PTEN-ASD. Answers to the latter questions can assist researchers and clinicians with developing specific recommendations for surveillance, interventions, and other supports. Finally, for identifying personalized therapeutic strategies that strongly impact the identified PTEN-ASD phenotypes and associated disability, it is crucial that future research identify the most important molecular and neural systems mechanism driving neurobehavioral dysfunction. This knowledge is key in the search for personalized therapeutic strategies.

To accomplish this ambitious research agenda, it is important that clinicians and researchers work together with PTEN patients and families. This is likely to involve strong relationships with existing PTEN patient foundations and developing new methods to efficiently enroll newly identified patients in research, including the use of digital medicine and online data-collection approaches to supplement traditional in-person medical and neurobehavioral evaluations. Digital health approaches will also facilitate longitudinal data collection without excessive patient burden. Ecological momentary assessment or experience sampling (Shiffman et al. 2008) can improve the granularity of longitudinal information and provide better data about how neurobehavioral dysfunctions impact daily life. Regardless of the methodology and objectives of future studies, ensuring that clinically relevant questions are being asked and answered and that information is translated to improved patient care and quality of life is necessary to maintain positive engagement in research from the PTEN community.

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