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Autism spectrum disorders: a review of measures for clinical, health services and cost–effectiveness applications

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Abstract

Autism spectrum disorders (ASDs) are characterized by impairments in social interaction, communication and behavioral functioning that can affect the health-related quality-of-life outcomes of the affected child and the family. ASDs have increased in prevalence, leading to a demand for improved understanding of the comparative effectiveness of different pharmacologic, behavioral, medical and alternative treatments for children as well as systems for providing services. This review describes outcome instruments that can be used for clinical, health services and cost–effectiveness applications. There is a pressing need to identify the most appropriate instruments for measuring health-related quality-of-life outcomes in this population. Studies evaluating the cost–effectiveness of interventions or treatments for children with ASDs using the cost per quality-adjusted life year metric are lacking. Researchers have the potential to contribute greatly to the field of autism by quantifying outcomes that can inform optimal treatment strategies.

Keywords

autism spectrum disorders; behavioral outcomes; children; clinical outcomes; economic evaluation; HRQL; preference-weighted scores

Autism spectrum disorders (ASDs) are complex neurodevelopmental conditions that involve impairments in social interaction, communication and behavioral functioning such as repetitive and stereotyped behaviors [1,2]. While individuals with ASDs are characterized

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by a core set of symptoms, there is wide heterogeneity in the severity of the disorder. Three subtypes are typically used to classify ASDs that include autistic disorder, Asperger's disorder and pervasive developmental disorder – not otherwise specified (PDD-NOS). Whether such categorical distinctions should be made is debatable and the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders criteria is likely to exclude this classification in favor of a single diagnostic category [201]. However, there is agreement that children with ASDs differ according to age and type of onset, severity and comprehensiveness of symptoms, and extent of language delay and intellectual disability [3].

Diagnosis of ASD subtypes requires a full understanding of a child's profile of abilities including developmental/cognitive, speech, language, communication, social, adaptive, sensorimotor and behaviors [4]. Owing to the wide range of abilities and limitations across clinical characteristic, clinicians may not reliably agree on the diagnostic subtypes of ASD – that is, clinicians may apply the specific diagnostic labels (autistic disorder, Asperger's disorder and PDD-NOS) differently across sites even when standardized clinical instruments are used [5]. Children who meet full diagnostic criteria for ASD are likely to be categorized as autistic disorder or classic autism, which typically is the most severe form [1]. Children with some symptoms of ASD but not enough to be diagnosed with autistic disorder are often diagnosed as having PDD-NOS. Asperger's disorder is the least severe ASD subtype and may be referred to as high-functioning autism. Children with Asperger's disorder have social impairments and autistic behaviors such as repetitive or restrictive patterns, but have intact cognitive ability (absence of intellectual disability) and no delays in early language development [6].

Autism is generally a lifelong condition beginning in childhood and affecting outcomes in adulthood. Outcomes describing difficulties or issues in finance, employment and socialization for adults with ASDs have been described previously [7–9]. Findings from these studies indicate substantial progress in the care and treatment of persons with ASDs, allowing individuals to participate more fully in community life with reduced burden on families. Despite these advances, living with autism can be difficult [10], particularly during developmental transition and critical need periods of childhood. While all children with ASDs exhibit one or more of the core symptoms (impairments in social interaction, communication and behavioral functioning), some children may have associated problems with mood and affect. They can exhibit severe tantrums, non-compliance, destructiveness and self-injury [11–13]. Children with ASDs may sleep less and awake frequently during the night [14–17]. Many parents report a regression in sociability, language and play during their child's toddler or preschool years. Therefore, parenting for some children with ASDs can be challenging and can severely impact family functioning as well as the health and wellbeing of caregivers and other family members [18,19]. Clearly, successful interventions for children with ASDs have the potential to greatly affect health outcomes for the child and can have extensive economic benefits by contributing to the child's independence into adulthood.

Interest in measuring health outcomes for children with ASDs has increased in recent years owing to reports of increasing prevalence. The prevalence of ASDs increased over the last two decades from four to ten per 10,000 children between the 1980s and early 1990s, and then to 30 to 50 per 10,000 children in the early 2000s [20–25]. In the USA, the Autism and Developmental Disabilities Monitoring Network reported an average of 1% or one child in every 110 had an ASD (males 1:70; females 1:315) in 2006 [26]. Indeed, the Interagency Autism Coordinating Committee calls the increasing prevalence of autism a 'national medical emergency' [202]. A recent population-based study found high prevalence rates of ASDs, with 3.7% in males and 1.5% in females in school-age children in a South Korean

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community that included samples from special-needs schools and regular school settings [27]. They reported that two-thirds of ASD cases in the overall sample were undiagnosed and did not receive any special services, suggesting that there are undiagnosed children with ASDs in regular classrooms. While much discussion has concerned the causes of the increasing prevalence of ASDs such as increased public awareness of ASDs, broadening ASD diagnostic criteria, increased availability of educational services and better identification, there is clear evidence that the burden of ASDs is large. School systems and medical care systems require increasing resources to treat the growing population of children diagnosed with ASDs. Therefore, there is a considerable need for research on treatment strategies that ensure that children with ASDs achieve optimal outcomes.

Despite advances in medicine, no medication is approved for an ASD indication owing to the lack of benefits on the core symptoms of ASD [28–30]. Only risperidone and aripiprazole demonstrated improvement in parent-reported measures of challenging behaviors such as repetitive behavior, hyperactivity and noncompliance. However, there are significant side effects that may limit the use of these drugs to patients with severe impairment or risk of injury [31]. There is evidence of efficacy for early intensive behavioral interventions (EIBIs) based on applied behavioral analysis [32]. EIBI is a comprehensive treatment approach that includes a minimum of 20 h per week of behavioral interventions from clinicians initiated at an early age (toddlers and preschool-aged children), and also involves parent training and parent delivery of at least 5 h per week [28]. The approximate annual costs of EIBI range from US$20,000 to $60,000 per child [33]. Owing to the cost of EIBI and knowledge gaps among providers, there is substantial variation in whether children receive recommended levels of therapy across geographic regions. Therefore research is needed to describe the impact of variations in treatment on outcomes of children with ASDs. Achieving this goal and obtaining the best information from randomized trials of pharmaceutical interventions requires an understanding of the various approaches for measuring health outcomes and selecting appropriate instruments suitable to the population of children with ASDs.

This article provides a review of health outcome measures for children with ASDs including clinical and behavioral measures, health-related quality-of-life (HRQL) measures and preference-based HRQL measures. The term ‘health outcome measures’ has been used to describe a broad range of instruments that can be used for clinical, health services and economic applications. In all of the applications, the instruments and the terminology reflect measures that can be used to study health outcomes from clinical trial settings or population-based registries. The review includes a discussion of preference-based measures to facilitate discussion of cost–effectiveness analysis – an approach that remains underdeveloped with respect to child health interventions [34–36]. Finally, new methods for cost–effectiveness analysis based on economic models that account for health outcomes of the family have been considered. Owing to the burden of ASDs on families, measures for estimating cost–effectiveness of interventions for the child with autism that account for impacts on the family have been included because both improvements in child and family health contribute to economic welfare [37].

Health outcome measurement in child populations is often accomplished by asking the parent to report on their perceptions of the child, owing to concerns that the child may not be able to respond reliably. A growing body of literature provides evidence for obtaining health outcome responses, or patient-reported outcomes, directly from the child [38]. Such an approach in autism is complicated as children (and adults) may lack a theory of mind that allows them to communicate health outcomes as measured by the instruments described in this review [39]. Theory of mind deficits are thought to underlie the core social and communication impairments that are characteristic of individuals with ASDs. Since children

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with autism may have theory of mind deficits and thus be less able to report health outcomes, recent research has examined whether adolescents with autism can report their quality of life (QoL) validly and reliably [40]. Initial findings for high-functioning adolescents indicate that it is feasible to get QoL responses directly from the adolescent. Additional research indicates that parent reports of QoL were closer to adolescents when parents were asked to report as they thought the child might respond [41]. Researchers interested in measuring health outcomes for children with ASDs need to consider these issues more fully, as parent proxy reporting is likely to be necessary for younger children and lower functioning children with autism who are more likely to have theory of mind deficits. This review focuses on the descriptions of health outcome measures and the studies that have employed them, recognizing that more work needs to be focused on the issues associated with proxy reporting of child health states in autism owing to the potential theory of mind deficits.

The authors acknowledge that there are multiple health outcome measures that can be used to study ASDs in children, and that any selection of instruments covering clinical, health services and cost–effectiveness applications is likely to be incomplete. The outcome measures selected for this review were based on instruments that have been used in recent randomized clinical trials and/or collected in ongoing registries of children with autism. Despite limitations in our ability to address a comprehensive listing of instruments, it is believed that readers will appreciate the potential for including all three types of measures in research studies involving children with ASDs.

Clinical & behavioral outcome measures

There are numerous assessment tools available to describe and assess core symptoms and behavioral outcomes for children with ASDs. Owing to space limitations, discussion of the more commonly or widely used instruments typically used to measure health outcomes in randomized trials or collected in ongoing registries of children with ASDs has been limited. Although many of the instruments described in this section are used in clinical settings to describe the symptoms and impairments of autism or to assess the severity of the condition for diagnostic purposes, they have been and continue to be used as outcome measures in research settings, especially clinical trials, and are described here.

ASD-specific measures

Autism Diagnostic Interview – Revised—The Autism Diagnostic Interview – Revised (ADI-R) is an extended structured interview conducted with a parent or caregiver to obtain the developmental history and current behaviors of an individual aged 2 years or above [42]. It comprises 93 items, which focus on three functional domains: language/communication; reciprocal social interactions; and restricted, repetitive and stereotyped behaviors and interests. The ADI-R is an effective tool to differentiate autism from other developmental disorders [43,44]. It focuses on the core deficits of ASD. Administration and scoring normally takes 90–180 min. The ADI-R focuses on behaviors that are rare in nonaffected individuals, and results are reported in a categorical manner rather than providing scales or norms.

Autism Diagnostic Observation Schedule and its Severity Score—The Autism Diagnostic Observation Schedule (ADOS) is a semi-structured autism observation measure that has become the gold standard for assessing autistic behavior and diagnosing ASDs across the age span, developmental levels and language skills [45]. It has been administered as part of autism registries (i.e., the Autism Treatment Network [ATN] initial comprehensive evaluation) and clinical trials [32,46]. The ADOS Severity Score is an overall measure of autism severity that can be constructed from scores on the ADOS [47].

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The ADOS Calibrated Severity Score provides a metric to quantify ASD severity with relative independence from the child's age and IQ. The raw ADOS totals can be mapped onto a 10-point severity metric. The Severity Score ranges from 1 to 10 with scores of 1–3 indicating a nonspectrum classification on the ADOS and scores of 4 and above indicating greater severity of autism on the ADOS. Administration and scoring of the ADOS and ADOS Severity Score generally take 30–60 min to complete.

The ADOS and ADI-R are both individually administered measures that focus on the core deficit behaviors of ASD; the former is administered with the person with ASD, and the latter with a parent or caregiver of the individual with ASD. Psychometric properties of both instruments have been reported [42,48,49]. The ADOS and ADI-R were developed as diagnostic tools, particularly for making differential diagnosis, and are more comprehensive in that they examine social, communication and behavior patterns characteristic of ASDs. However, both instruments require extensive training and practice before they can be administered, especially the ADOS, and are commonly administered by a psychologist or speech/language pathologist.

Childhood Autism Rating Scale—The Childhood Autism Rating Scale, Second edition (CARS2) is a clinician-completed behavior rating used to identify and distinguish children with ASDs from other developmental disorders, as well as to determine ASD symptom severity [50]. The instrument is valid and reliable across time and raters [50]. The CARS2 has two different forms for clinicians based on information that is gathered from parents or caregivers (CARS2-QPC). The two forms are CARS2-ST, which is used with children younger than 6 years of age and those with communication difficulties or below-average estimated IQs, and CARS2-HP, which is an alternative for assessing verbally fluent individuals or children 6 years old or above, or children with IQ scores above 80. The revised edition expands the tests from the original CARS to cover high-functioning autism or Asperger's disorder, making it more responsive to those with more subtle social impairments and behavioral problems. The CARS2 has 15 items that can be administered in 5–10 min. The CARS2 focuses on core deficit behaviors.

Generic measures

Aberrant Behavior Checklist—The Aberrant Behavior Checklist (ABC) is a behavior rating scale that is completed by the parent or primary caregiver of the individual with ASD. The ABC was originally developed for assessing treatment effect in individuals with cognitive disability [51]. It is a useful tool to evaluate maladaptive behaviors such as ASD symptoms. The ABC includes some core deficit behaviors as well as associated symptoms of ASD. It has 58 items that are scored on five subscales that include irritability, agitation, crying, lethargy, social withdrawal, stereotypic behavior, hyperactivity, noncompliance and inappropriate speech. The ABC can be used for individuals between 5 and 54 years of age with an administration time of 10–15 min. The ratings are made with consideration to the child's behavior over the previous 4 weeks. Higher scores on the ABC indicate more severe problem behaviors. The ABC presented good internal consistency, test–retest reliability, and inter-rater reliability as well as validity [51].

Child Behavior Checklist—The Child Behavior Checklist (CBCL) is a standard measure of externalizing (i.e., aggressive, hyperactive, noncompliant and undercontrolled) and internalizing (i.e., anxious, depressive and overcontrolled) behavior problems using parents' ratings of 99 items [52,53]. The total scaled scores, which are expressed as T-scores (mean of 50; standard deviation of 10), can be used to report children's behavior problems including total problems, total internalizing and total externalizing scores. Parents should be able to complete the instrument in 10 min. The CBCL covers a wide range of behavior

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symptoms. It may be especially useful for measuring symptoms related to psychiatric comorbidities in children with ASDs. The CBCL focuses on associated symptoms, not core deficit behaviors. The instrument has good psychometric properties [53].

The Vineland-II Adaptive Behavior Scales—The Vineland-II Adaptive Behavior Scales (VABS) is a useful tool to capture adaptive functioning [54]. The VABS consists of four major domains: communication, socialization, daily living skills and motor skills (age <6 years), all of which contribute to an adaptive behavior composite score, as well as an optional maladaptive behavior domain. The VABS produces an adaptive behavior composite score, domain and subdomain scores, and age equivalents. The instrument also has supplementary norms for children with autism [55]. The VABS-II demonstrated good psychometric properties including internal consistency, inter-rater reliability and content validity [54].

The VABS can be administered by either an interview that takes approximately 45–60 min for a clinician to complete with the primary caregiver of the individual with ASD, or a parent/caregiver rating form. It does not require the presence of the individual being assessed. The VABS can be used across a broad range of conditions and focuses on the current level of functioning. In contrast to cognition, which is usually viewed as relatively more stable for most individuals over time, adaptive functioning is considered modifiable. The VABS may thus be particularly useful to assess the effects of various treatments or clinical interventions on levels of adaptive functioning.

Social Responsiveness Scale—The Social Responsiveness Scale (SRS) is a 65-item rating scale completed by a parent or teacher that assesses severity of symptoms associated with ASDs along a continuum [56]. The SRS provides a picture of a child's social impairments, yielding an overall severity score (a higher score corresponds to greater impairment). It assesses social awareness, social information processing, capacity for reciprocal social communication, social anxiety/avoidance, and autistic preoccupations and traits. It is appropriate for use with children aged 4–18 years. The SRS can be used as a screener in clinical or educational settings, an aid to clinical diagnosis or a measure of response to intervention. It yields a total score reflecting the degree of overall social impairment; the scale can detect subthreshold autistic symptoms that may be relevant in evaluating children with a wide variety of psychological problems. The SRS distinguishes children with ASDs from other child psychiatric conditions [56–58].

Repetitive Behavior Scale – Revised—Restricted, repetitive and stereotyped behaviors are characteristic of the fixated behavior patterns that occur in children with ASDs. Moreover, these symptoms are related to the severity of the ASD condition. The behaviors can be measured using the Repetitive Behavior Scale – Revised (RBS-R) [59]. The RBS-R is a quantitative, empirically derived clinical rating scale. It measures both the presence and severity of repetitive behaviors, and provides a continuous measure of the full spectrum of repetitive behaviors. Parents are asked to rate their children's behavior on 42 items. The measure contains six subscales that have no item overlap: stereotyped behavior, self-injurious behavior, compulsive behavior, routine behavior, sameness behavior and restricted behavior. A total score is generated, with higher scores indicating more restricted, repetitive and stereotyped behaviors. The RBS-R has been reported to have adequate psychometric properties and acceptable reliability and validity for each subscale [59,60]. The RBS-R measures some of the core deficit behaviors as well as associated behavior symptoms of ASD.

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Cognitive measures—Cognitive ability for children with ASDs can range from low to high across any range of severity for the condition [61,62]. Developmental patterns in children with ASDs can be influenced by age and IQ [63]. For example, lower IQ may interact with the severity of the child's autism to increase the need for assistance with activities of daily living. There are several existing cognitive measures that have been used in psychology and educational studies. In this review, the authors focus on measures used in ASD clinical studies. The tools included in this review are the Stanford–Binet Intelligence Scales (5th Edition), the Mullen Scales, the Bayley Scales and the Wechsler Intelligence Scales. All of the scales have good psychometric properties [64–67]. The Stanford–Binet Intelligence Scale is an individually administered formal test of general intelligence used with individuals aged 2–89 years and yields an IQ value. In young children, the Mullen and the Bayley Scales are commonly used measures that examine the child's cognitive development. The Mullen Scale is an individually administered comprehensive measure of cognitive functioning for children from birth through 68 months of age and yields a cognitive composite score, the Early Learning Composite. The Bayley Scale is an individually administered comprehensive measure of cognitive functioning for children from birth through 42 months of age and produces a cognitive score. The Wechsler Intelligence Scales for Children – Fourth Edition is appropriate for children and adolescents aged 6–16 years. It provides four index scores (verbal comprehension, perceptual reasoning, working memory and processing speed) and the full scale IQ. All four cognitive measures yield an overall composite score that is expressed as a standard score with a mean of 100 and standard deviation of 15 to describe an individual's cognitive ability and are comparable measures of general intelligence.

Applications using clinical & behavioral measures

Both the ASD-specific and generic measures have been used as end point outcomes in several randomized controlled trials of psycho-pharmacology in children with ASDs with a focus on behavioral symptoms [30]. For example, the Research Units on Pediatric Psychopharmacology Autism Network used the ABC subscales (irritability and hyperactivity subscales) as outcome measures to determine efficacy of medications such as atomoxetine, risperidone and methylphenidate for controlling irritability and hyperactivity symptoms in children with autism [68–70]. Improvement of the CARS has also been used as a primary end point to determine efficacy of risperidone in randomized controlled trials [71,72]. Belsito *et al.* determined the efficacy of lamotrigine in 28 children with ASD using the ABC, the VABS, the ADOS and the CARS as outcome measures [73].

In addition to use in trials of psychopharmacologic treatments, the clinical and behavioral measures described above have also been used for evaluating efficacy of behavioral services. For instance, one important clinical trial collected standardized clinical and behavioral outcome measures using trained (and blinded) interviewers to evaluate the Early Start Denver Model, an EIBI [32]. The trial used the Mullen Scales and the VABS as primary outcome measures to determine the effect of the intervention. The ADI-R, ADOS severity scores and the RBS were used as the secondary outcomes measures in the same study [32]. The trial reported an increase in IQ scores of 17 points as well as an improvement of the VABS composite scores in the intervention group. However, they did not find any differences in the ADOS severity scores or RBS total score between the two groups.

Clinical and behavioral outcome measures have several advantages and disadvantages. The major advantage of these measures is that they can be used as clinical end points in clinical trials since they measure changes in the core and ASD-related symptoms. There are three major disadvantages associated with clinical and behavioral measures. The first issue

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concerns the cost of administration owing to the time required to obtain them, and the potential need for trained interviewers or clinical observation. Second, some clinical measures such as the ADI-R, ADOS, ADOS severity and cognitive measures are designed to be more stable over time so they may not be sensitive to changes from interventions. Moreover, clinical and behavioral measures may be limited in their ability to inform resource allocation decisions. To address some of the limitations of clinical measures, the next section reviews HRQL measures that may be applicable for clinical and health services research studies involving children with ASDs.

HRQL outcome measures

The measurement of general HRQL in children has improved dramatically over time with the development of several instruments specific to pediatric populations, particularly the NIH-initiated Patient Reported Outcome Measurement Information System [74,203] and the Pediatric Quality of Life Inventory™ described below [75]. The use of HRQL instruments in children is increasingly adopted in clinical trials as it permits standardized measurement across studies and conditions [38]. Clinicians and policy makers can use information from HRQL measures to understand deficits in specific outcome domains. Treatments and interventions can then be targeted to improve health outcomes. Despite widespread acceptance of HRQL measurement in child populations, their applicability in children with ASDs remains understudied.

The behavior problems of children with ASDs can be categorized into two groups: core deficit behaviors and associated symptoms [76]. The associated symptoms may include hyperactivity/inattention, aggression (i.e., tantrums, self-injury, anxiety and emotional liability), obsessive–compulsive-like behaviors and sleep disorders. These impairments impact a child's QoL and HRQL. While a number of HRQL measures are available, this section reviews the selected HRQL instruments that appear to have potential for use in children with ASDs (Table 1). A review of the Patient Reported Outcome Measurement Information System instruments were not included, as the item banks for children and young adults with disabilities remains under development [204]. An ongoing review of the Patient Reported Outcome Measurement Information System instruments for children and youth as the item bank development for children and young adults with disabilities is not included [204]. The relevance of questions or domains of each HRQL instrument to the ASD core and associated symptoms/behaviors is based on the authors' opinions.

Pediatric Quality of Life Inventory™

The Pediatric Quality of Life Inventory™ (PedsQL) consists of 23 items that are designed for use in children aged 2–18 years [75]. It offers four age-appropriate versions for parent proxy-report (ages 2–4, 5–7, 8–12 and 13–18 years) and three age-appropriate versions for child self-report (ages 5–7, 8–12 and 13–18 years). The PedsQL includes four multidimensional scales (physical, emotional, social and school functioning) and three summary scores (total scale, physical health summary and psychosocial health summary scores). The instrument takes approximately 4 min to complete. All versions have a 1-month recall period. Each item of the PedsQL is converted into a 0–100 scale and a higher score indicates a better HRQL. The PedsQL also offers disease-specific modules such as asthma, rheumatology, diabetes, cancer and cardiac conditions. Unfortunately, it does not have a module on ASDs. The instrument has good psychometric properties among healthy populations as well as children with chronic conditions [77]. Recent research showed that the PedsQL demonstrated feasibility, reliability and validity among a pediatric population with psychiatric disorders [78].

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KIDSCREEN-27

The KIDSCREEN-27 is a generic HRQL assessment for children and adolescents aged 8–18 years [79]. The instrument can be used to measure burden or disability of particular diseases that affect children and adolescents' HRQL. The KIDSCREEN-27 has five Rasch scaled dimensions including physical wellbeing (physical activity, energy and fitness), psychological wellbeing (positive emotions, satisfaction with life and feeling emotionally balanced), autonomy and parents (relationships with parents, the atmosphere at home, feelings of having enough age-appropriate freedom and degree of satisfaction with financial resources), peers and social support (relationships with other children/adolescents), and school environment (perceptions of cognitive capacity, learning and concentration and feelings about school). It has a 1-week recall period. The KIDSCREEN demonstrated good psychometric properties in large samples of children and adolescents across European countries [79]. Completing the KIDSCREEN-27 takes 10–15 min.

Child Health Questionnaire

The Child Health Questionnaire (CHQ) was developed specifically for children and adolescents. It focuses on aspects of a child's health that might impact family functioning as well as behavior problems and self esteem of a child [80]. The CHQ has two forms, which include the 28-item parent-reported questionnaire (CHQ-PF28) for young children aged 4–11 years and the 87-item child form (CHQ-CF87) for adolescents aged 10 years or above. The CHQ-PF28 is divided into 13 domains including physical functioning, emotional/behavior role functioning, physical role functioning, bodily pain, general behavior, mental health, self esteem, general health perceptions, parental impact (emotional), parental impact (time), family activities, family cohesion and change in health. The CHQ-CF87 has 12 domains, which are the same as the proxy form except for the parent impact domain. Each domain and scale are transformed into a 0 (worst possible) to 100 (best possible) score. Both forms of the CHQ established feasibility and good psychometric properties in representative samples [81,82].

Health Status Questionnaire

The Health Status Questionnaire was developed for routine assessment for determining impairment and disability in high-risk children aged 2 years or older. It has eight clinical domains that include malformation, neuromotor function (walking, sitting, hand use and head control), seizure, hearing, communication, vision, cognitive and other physical disability (respiratory, gastrointestinal, renal and growth). The Health Status Questionnaire does not provide a summary score or value to evaluate the impact of the problem on a child's health but rather identifies impairment or level of disability of the child [83].

Child Health and Illness Profile

The Child Health and Illness Profile (CHIP) was developed for children and adolescents aged 6–17 years. It is intended to characterize the potential for resilience, satisfaction, risk avoidance, future health and achievement [205]. The instrument contains 107 items. It has two age-appropriate versions: child and parent (CHIP-CE) and adolescent (CHIP-AE). The parent report form can be used in tandem with the CHIP-CE to describe children's health from the parent's point of view. Health status of children and adolescents obtained from the CHIP is reported in standardized scores (domain level and total score), and higher scores indicate better health. The CHIP reliably and validly assesses the health status of children and adolescent populations [84,85].

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Functional Status II-R

The Functional Status II-R (FS II-R) is the revised version of the FS-I [86]. It was designed to measure behavioral manifestations of an illness or condition that interferes with a child's performance of the full range of age-appropriate activities. The FS II-R contains eight domains including communication, mobility, mood, energy, play, sleep, eating and toileting patterns. It can be used to determine whether difficulties in the child's functioning are attributable to the presence of the child's health condition. Both short (14 items) and long (43 items) FS II-R versions have good psychometric properties that were tested in a sample of children aged 2 weeks to 16 years.

Applications using HRQL instruments

There is limited information describing whether these instruments are actually sensitive to behavior problems in children with ASDs. The relevance of several domains included in HRQL instruments in relation to impairments associated with the core and associated features of children with ASDs has been reviewed (Table 1).

Although several good HRQL instruments are available, little research on HRQL outcomes has been conducted in children and adolescents with ASDs. Recent research has begun to identify the best methods for conducting HRQL assessment in adolescents with ASDs but the findings are limited to high functioning children [40,41]. To the authors' knowledge, only three studies report HRQL outcomes in cohorts of children and adolescents with ASDs [87–89]. Limbers *et al.* explored HRQL and cognitive functioning of 22 children with Asperger's syndrome aged 6–12 years using the parent proxy-report version of the PedsQL 4.0 Generic Core Scales and the Cognitive Functioning Scale [89]. They found that the PedsQL was able to distinguish between children with Asperger's disorder and healthy children. The HRQL and cognitive functioning scores were significantly lower in children with Asperger's.

Kuhlthau *et al.* examined HRQL outcomes for 286 children with any one of the three subtypes of ASDs enrolled in the ATN [87]. HRQL outcomes were examined with the PedsQL 4.0. Survey responses to the PedsQL were linked with clinical data describing the child's cognitive ability, adaptive functioning, ASD-related symptoms and behavior problems. The study showed that children with ASDs had lower HRQL outcomes in all domains of health including physical, psychosocial, emotional, social and school functioning when compared with healthy children. In addition, ASD-related symptoms were associated with decrements in HRQL outcomes.

Kamp-Becker *et al.* evaluated HRQL in 42 children and adolescents with ASDs and compared them with referent samples (healthy controls and children with other psychiatric disorders) using the Inventory for the Assessment of Quality of life in Children and Adolescents (ILK) questionnaire [88]. They reported that the self-reported mean ILK scores from the ASD sample were at the 47th percentile compared with the healthy sample and at the 67th percentile compared with the psychiatric sample. The HRQL outcomes of children and adolescents with ASD appeared to be better than in children with other psychiatric disorders, but lower than HRQL outcomes in population-based samples. Unfortunately, the ILK questionnaire is not currently available in an English version.

Although existing HRQL instruments have limitations in measuring HRQL for children with ASDs, they have the potential to capture some relevant behavior problems. For example, a number of the question items of the FS II-R such as play games, restless, trouble with task and sleep are relevant to ASD conditions. Therefore, the FS II-R might be a good candidate instrument (in addition to the PedsQL) to capture HRQL outcomes of children with ASDs. It is suggested that autism researchers should consider using more than one instrument to

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reflect all possible behavior problems in children with ASDs. In summary, HRQL measures should be included in clinical and health services research involving children with ASDs to evaluate the influence of interventions and services.

Preference-based HRQL outcome measures

Measuring HRQL as described above cannot provide information necessary for establishing the cost–effectiveness of services provided to children with autism. Such information is needed because financing services for children with autism depends largely on the perceived cost–effectiveness of treatment. Little is known about the cost–effectiveness of treatment services for children with ASDs, especially across the spectrum of disorders and associated heterogeneity in intellectual disability. Studies that attempt to assess the cost–effectiveness of services for children with autism are limited, especially using methods outlined by the US Panel on Cost–Effectiveness [90]. A central recommendation of the panel was to use the cost per quality-adjusted life year (QALY) as the metric for reference case analyses [91]. QALYs are measured as the amount of time in a health state weighted by a preference score or utility value that ranges from 0 (representing death) to 1 (representing perfect health) [92]. Under this approach, the value of increased spending for autism services can be compared to additional spending for other mental or physical health services because they are all measured on the same metric as cost per QALY gained.

The US Panel on Cost–Effectiveness recommended that utilities or preference scores are measured with generic instruments or are capable of being compared to generic instruments [91]. Several generic instruments are available for preference-weighting health outcomes, but a number of methodological problems are encountered when applying the panel's recommendation to children [93]. Children may not be able to respond to the instrument because of their reading comprehension level, or may be too young to be a valid respondent [34,35]. These issues are further compounded in children with ASDs as they may not be communicative or may have theory of mind deficits [39].

Many of the available instruments ask about usual activities such as school or work, so most researchers do not attempt to measure preference scores in children with generic instruments below the age of 5 years. In addition, the health domains associated with various instruments may not be applicable to children or may not be developmentally appropriate. For these reasons, cost–effectiveness evaluations of childhood conditions that used QALYs have been described as 'lacking quality' [94]. Relative to adults, little research has compared findings across different preference-weighted instruments in pediatric populations [95].

There are several preference-based HRQL instruments in the literature. The most popular instruments include the Quality Well-Being (QWB), the EuroQol five-dimension questionnaire (EQ-5D), the 6-dimension Short Form (SF-6D), the Health Utilities Index (HUI) Mark 2 and 3, and the Assessment of Quality of Life (AQoL). Most of the instruments were developed without consideration for use in children, with the exception of the HUI2. All of the instruments, however, have been used in studies of children and adolescents with the exception of the SF-6D [95–99]. Because there is newfound interest in economic evaluations of child health interventions [100], two preference-based HRQL instruments that specifically pertain to children and adolescents were recently developed: the EQ-5D youth version (EQ-5D-Y) and the Child Health Utility 9D (CHU9D) [101,102]. This section describes instruments for preference-weighting health outcomes that have been used in child and adolescent populations irrespective of whether they were developed specifically for use in children and adolescents or not. Using the same approach described in Table 1**,** a list of preference-based HRQL instruments in relation to ASD behavior problems has been provided (Table 2).

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The HUI

The HUI is a family of preference-based systems that include HUI2 and HUI3 instruments. It is used to measure health status that can be reported as HRQL outcomes and preference-weighted scores. Both the HUI2 and HUI3 include a generic health profile and a generic preference-based scoring function. The HUI2 has seven domains including sensation, mobility, emotion, cognition, self care, pain and fertility, with three to five response levels in each domain. It describes 24,000 unique health states. The HUI3 includes eight domains – vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain – each with five or six response levels. It defines 972,000 unique health states. Both instruments allow for negative preference-weighted scores (worse than dead). The lowest possible scores are −0.03 for HUI2 and −0.36 for HUI3. HUI instruments can be used in children aged 5 years and older (proxy assessment for children age 5–12 years). Per the HUI developers, HUI3 should be used as a primary measure as it has structural independence among domains, which makes its descriptive system more efficient compared with HUI2 [97].

Although some domains on HUI2 and HUI3 have the same name, they have different underlying constructs. For example, the HUI2 emotion domain asks about irritability, depression and anxiety, while the HUI3 emotion domain asks about level of happiness. Similarly, the HUI2 cognition domain asks about learning ability appropriate for age but the HUI3 cognition domain focuses on the ability to solve day-to-day problems. The two systems are independent but complimentary. For measuring outcomes of children with ASDs, the HUI2 may have some advantages over the HUI3, such as emotion (i.e., irritability, anxiety, night terrors and anger), cognition (i.e., learning ability) and self-care (i.e., eats, bathes, dresses, uses the toilet independently). On the other hand, the HUI3 has a separate domain on speech, which is one of the most important impairments found in children with ASDs.

The QWB Scale

The QWB self-administered version (QWB-SA) combines three scales of functioning – mobility, physical activity and social activity, including completion of role expectation – with a measure of symptoms and problems (58 symptom/problem complexes; CPX) to produce a point-in-time expression of wellbeing that ranges from 0 (for death) to 1.0 (for asymptomatic full function) [103]. The instrument has a 3-day recall period. Some questions on the CPX, such as hangover and sexuality, are not relevant for children, and researchers need to consider leaving out these items or consider other solutions when using this instrument in child populations.

The AQoL Mark 2

The AQoL Mark 2 includes six dimensions (AQoL-6D): independent living, social and family, mental health, coping, pain and senses. The AQoL-6D for Adolescents has been recalibrated to derive preference-weighted scores specifically for adolescents in four Pacific countries (the Pacific Obesity Prevention in Communities project) [104]. The AQoL-6D for Adolescents has the same items as the original AQoL-6D with slight modification.

The EQ-5D-Y

The EQ-5D-Y is a child-friendly version of the EQ-5D. The language and content were modified to be relevant and appropriate for children aged 8 years or older [101]. The descriptive system of the EQ-5D-Y is the same as the adult version EQ-5D with three levels of responses. It includes five questions on mobility, self care, usual activities, pain/discomfort and anxiety/depression on current health status. Feasibility and psychometric

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properties of the EQ-5D-Y have been demonstrated in children and adolescents in several countries [105].

The CHU9D

The CHU9D was specifically developed for a pediatric population aged 7–11 years [102,106]. It contains nine questions covering nine dimensions of HRQL (worried, sad, pain, tired, annoyed, school-work, sleep, daily routine and activities). The CHU9D focuses on current (today/last night) health status with five response levels in each question. Recent research shows that the CHU9D has good psychometric properties and can distinguish children with a wide range of health problems from general pediatric populations. A proxy version of the CHU9D has been developed and is currently under testing for use in younger children. Although the CHU9D has not been used in children with ASDs, it has several domains that are relevant to ASD symptoms such as annoyed, schoolwork, sleep, daily routine and activities.

Applications using preference-based HRQL instruments

To our knowledge, only two published studies have reported on preference scores for children with autism, and both studies used the HUI3 [107,108]. Petrou and Kupek identified families of children with autism and other childhood conditions from a database consisting of children with disabilities and severe illness that applied to a fund for support [107]. Out of a total sample of 2236 returned surveys, 105 children with ASDs were identified. Among these children, the HUI3 scores averaged 0.43 and differed from childhood norms by −0.37 to −0.62 points. Petrou *et al.* also reported HUI2 and HUI3 scores among children with psychiatric disorders using a sample from a population-based longitudinal study of extremely preterm children and term-born controls (the EPICure study) [108]. Only 11 children with autistic disorder were included in the study. The average HUI2 and HUI3 scores were 0.72 (standard deviation [SD] = 0.15) and 0.61 (SD = 0.26), respectively.

Preference-based data have not been reported on ASD subtype, associated cognitive functioning or other clinical characteristics of the child. Therefore, the only available published evidence on preference weights for children with ASDs that could be used in cost–effectiveness analyses is limited to information that can be applied to the complete prevention of autism. No information on utility weights for children with autism is available that can be used to inform the potential for behavioral or medical treatments to prevent the symptoms of autism and thus assist with prioritizing services. In order to test the sensitivity of generic preference-weighted instruments to capture changes in the clinical characteristics of children with ASDs to assist in cost–effectiveness analysis [92], Tilford *et al.* combined parent-reported HUI3 and QWB scores with clinical data for a sample of children enrolled in the ATN [109]. Clinical data were obtained at the time of diagnosis and mailed surveys were sent to families that consented to participate and who were part of the registry. Tilford *et al.* found that the HUI3 scale was more sensitive to changes in clinical characteristics relative to the Quality of Well Being scale [109]. Other instruments were not considered because they were not available at the time the study began. The average HUI3 score in the full sample was 0.66 (SD = 0.23). Children with Asperger's syndrome had significantly higher HUI3 scores (0.79 ± 0.16) compared with children with PDD-NOS (0.70 ± 0.24) and autistic disorder (0.64 ± 0.23). The largest gains in preference scores were found with improving language outcomes. Including the HUI3 in clinical trials and other services' research projects is recommended to develop the evidence base for providing cost-effective interventions in this population.

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Incorporating family effects in cost–effectiveness analysis

Economic evaluations of health services typically take a unitary perspective where outcomes of treatment are measured solely on the patient – in this case, the child with an ASD. However, services for children with ASDs that improve their health outcomes also have the potential to improve the health and wellbeing of other family members. Therefore, effective services that improve outcomes for children with autism may have substantial 'spillover effects' on the family [18,19]. The need to incorporate family effects in cost–effectiveness evaluations is increasingly recognized, but there is little evidence or guidance regarding the best way to include such effects [110]. Failure to incorporate family effects in economic evaluations has the potential to understate the benefits of effective interventions.

Methods to incorporate family effects in economic evaluations are being developed. Basu and Meltzer [37], and Basu *et al.* [111] provided necessary theoretical guidance to focus the discussion of family effects and economic evaluation. The models demonstrate that in the case where family spillover effects may be present, QALYs should not be calculated solely on the gains in utility to the child associated with additional services, but should also incorporate gains to the family associated with services provided to the child. A number of empirical approaches for measuring health effects of caregivers or family members have been advanced in the literature, which has been briefly reviewed in the next section. For a more detailed discussion see [112].

Empirical approaches to incorporating family effects in cost–effectiveness analysis

The negative health effects associated with caregiving were illustrated in a number of studies where the main measure of HRQL was the Center for Epidemiologic Studies Depression Scale [113,114]. The Center for Epidemiologic Studies Depression Scale, however, like other HRQL measures, cannot be incorporated into economic evaluations either as a monetary value for cost–benefit analysis or as a QALY for cost–effectiveness analysis. Therefore, recent approaches seek to estimate health or wellbeing effects on caregivers or other family members that can be included as economic variables.

One interesting approach to measuring impacts on 'significant others' – family members or persons related to the patient in a way that the patient's health influences the other's health or wellbeing – separates health and wellbeing effects into a caregiving and a family effect [115,116]. The caregiving effect is defined as the impact of caregiving tasks on caregiver health. This effect is limited by construction to those involved in caregiving tasks. As caregiving tasks become more burdensome, one expects a negative impact of caring on health for those involved in providing care to the child. By contrast, the family effect can apply to caregivers as well as 'significant others.' Family effects are present when health or well-being for significant others improves because of improved health of the child or patient. These effects may apply more broadly to parents, siblings and other people related to the child. Bobinac *et al.* demonstrated the importance of both effects in a sample of patients and caregivers with chronic conditions [115,116]. One can easily see the applicability of the model applied to children with ASDs and their families. Effective interventions that reduce caregiver burden can produce a health effect on caregivers, but may also entail health or wellbeing effects for extended family members and significant others.

A number of different approaches and measures of health and QoL can be used to estimate family impacts. In the studies of Bobinac *et al.*, caregiver QoL was measured by a 'happiness' scale based on a simple visual analog scale [116] and a preference-based measure: the visual analog scale from the EQ-5D [115]. Preference-based measures of health can be directly incorporated into economic evaluations because they can be used to

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measure QALY gains. Similar to the literature on distinguishing which generic instrument works best to describe health outcomes of the child or patient, however, there is a need to understand which generic instrument might be best suited to describe the health outcomes of family members or significant others. Payakachat *et al.* examined the sensitivity of three generic instruments to measure health outcomes of caregivers of children with craniofacial malformations [117]. Much more work is needed to determine the most effective instruments that could be used to understand the full impact of treatment interventions for children with ASDs on caregivers or other family members.

Another approach for measuring caregiver health outcomes involves asking caregivers how caring affects their QoL. The Care-related Quality of Life (CarerQol) instrument was developed with the intention of having a practical administration method to measure caregiver QoL that can subsequently be used in the context of economic evaluation [118]. The CarerQol comprises two parts: the CarerQol-7D and the CarerQol-VAS The CarerQol has seven items (fulfillment with care tasks, relational problems with care receiver, problems with own mental health, problems with combining care tasks with daily activities, financial problems owing to care tasks, support with care tasks and problems with own physical health) that measure the impacts of caregiving. The CarerQol-7D allows caregivers to indicate their caregiving burden with respect to each particular dimension on one of three levels and potentially distinguishes 2187 different care situations. The CarerQol-VAS is a visual analogue scale measuring overall happiness ranging from 0 (completely unhappy) to 10 (completely happy). The instrument presented good construct validity in a Dutch sample of heterogeneous caregivers [118], as well as caregivers for children with craniofacial malformations [117].

In contrast to indirect measurement of caregiver health and wellbeing based on experienced health states, several studies have employed methods to capture family spillover effects using direct elicitation techniques. One direct elicitation approach is to ask caregivers to consider how much time they would trade-off at the end of their remaining life expectancy to prevent a childhood condition [119,120]. The amount of time the parent is willing to trade divided by the remaining life expectancy can be used to form an estimate of QALYs lost due to the condition that incorporates both the impact on the child and the impact on the parent.

Other researchers have asked caregivers or significant others to trade-off life years associated with living with a patient who has a medical condition taking into account only the effect of the patient's condition on their own life. Basu *et al.* developed this technique for spouses and partners of men being evaluated or treated for prostate cancer [111]. Spouses/partners were asked to trade-off time associated with different health states affecting the patient, but again only taking into account the impact on themselves and not the patient, as health states affecting the patient can be obtained separately. This method can be extremely useful, especially for estimating family effects associated with the death of the patient.

Employing time trade-off measures for incorporating health states affecting family members associated with conditions in children with ASDs is likely to create a number of potential measurement issues that will need to be addressed. Asking family members to trade-off time associated with the child's condition, whether or not they take into account the impact on the child or just themselves, also raises issues. Caregivers recognize the needs placed on them by their child and have difficulty separating the hypothetical task of giving up life years with the need to be available to take care of the child. Caregivers also indicated a major difficulty in trying to isolate impacts of their child's condition as it pertains to their own health. For example, caregivers would be willing to give up a large portion of remaining life expectancy

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for their child to be able to communicate, but it reflects their interest in improving health for the child [121].

Whether direct or indirect elicitation techniques will or should be used to incorporate impacts on the family in economic evaluations remains an open question. Both approaches have issues that need to be addressed and they provide different information for policy. The important message is that children with ASDs face a number of challenges and, if they receive effective treatments, they are likely to experience an improvement in their HRQL. This improvement in HRQL has the potential to substantially affect family members and significant others, and all analysts should be cognizant of this fact and develop appropriate methods to account for family effects whether measured in clinical settings or in policy contexts.

Expert commentary

Historically, physicians were taught that autism was a rare condition but that they should be aware of it in case they encountered a child with the associated symptoms at some point in their practice. This view of autism changed dramatically with the rapid rise in the reported prevalence of ASDs that occurred over a relatively short time span. The increased prevalence of children with ASDs increased the demand for services and associated costs in both medical and educational settings, due in large part to the burden of the condition on families and reports in both professional and lay literature that different treatments could prevent the symptoms of autism or lead to full recovery in a significant percentage of affected children [122,123]. Therefore, there is now a significant need to understand the value of services by identifying relationships between spending on services to treat children with ASDs and health outcomes. By identifying relationships between spending on services for ASDs and outcomes, it may be possible to optimize health outcomes for children with ASDs. Research in this area is limited and can only be characterized as in its infancy. Consequently, services for children with ASDs are characterized by wide variations across states and municipalities, with a large proportion of children in some areas receiving intensive behavioral services and in other areas just the opposite.

This review provides researchers with descriptions of a wide array of measures to address relationships between service use and health outcomes for children with ASDs in clinical, health services and cost–effectiveness applications. Our review indicates that a number of measures are available with excellent properties that can be used effectively. All of the measures have different attributes that provide both advantages and disadvantages associated with the special requirements for measuring health in children, especially children with ASDs. Many children with ASDs may not be able to describe their health state reliably due to cognitive and behavioral impairments that lead to theory of mind deficits, and thus researchers must rely on parent or clinical observation for useful information. New research on eliciting health outcomes of children with ASDs provides valuable direction for future studies [39,40].

The need to use parent or clinical observation to measure health outcomes in children with ASDs raises a number of issues. In clinical trials where it is not possible to blind parents to treatment arms – intensive behavioral services, for example – use of parent-reported health measures may lead to biased estimates of the treatment effect. For this reason, outcome measures in clinical trial settings use trained observers to obtain the generic and ASD-specific measures described above. The need to obtain measures by trained observers greatly increases the cost of research and limits the number of participants that can be enrolled in a trial. If parent-reported HRQL estimates can be made to correspond to findings from clinical observation, it would be possible to increase the number of participants in clinical trials,

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provide more stable estimates of treatment effect and allow comparisons to established norms. Clearly, there is a significant need for correlating ASD-specific outcome measures obtained by clinical observation and child or parent-reported HRQL measures from clinical trials. Inclusion of parent-reported measures of preference-weighted outcomes would also have the advantage of providing information that could be used in cost–effectiveness analysis.

Since clinical trials require controlled settings and relatively small sample sizes, they may not generalize to real world settings where the provision of services cannot be controlled. Observational studies can exploit natural variation in services to estimate treatment effects using advanced statistical techniques that account for observed and unobserved heterogeneity across subjects [124–126]. For these study designs, it will again be useful to have both clinical measures and parent-reported outcome measures. A major hypothesis that has yet to be tested involves whether communities with better systems to finance and provide medical and behavioral services lead to improved access to these services and better outcomes for children with ASDs. Quantifying the extent of improved outcomes that can inform state and federal policies is vital. Owing to the burden of autism on families and the larger society, healthcare and educational systems that fail to achieve independent living skills for children with autism, if such outcomes are possible through better access to services, represent gross failure and inefficiency and require reform.

Testing whether different systems of care provide improved outcomes for children with autism is unlikely to be accomplished by clinical trials and must rely on observational designs. This review provides an indication of the necessary measures that will need to be obtained to test the hypothesis and evaluate whether the additional spending required to provide additional services is likely to be a cost-effective investment of society’s resources. We believe that any evaluation of the cost–effectiveness of services for children with ASDs must take into account the potential for improved outcomes on the child to improve outcomes for caregivers and families. Failure to account for these effects in economic evaluations will understate the benefits of improved outcomes associated with increased spending on services.

Five-year view

In the next 5 years, there will be a dramatic increase in resources to fund studies to identify optimal treatment strategies for children with autism. While a significant number of these studies will be in the form of clinical trials, research on the comparative effectiveness of different systems to provide services for children and families affected by autism will be observational in design. In both clinical trial and observational settings, researchers need the best instruments to inform policy. Much research needs to be conducted to identify the instruments with the best potential to inform diverse groups of stakeholders.

There is limited information on which HRQL instruments could be used to measure HRQL outcomes for children and families affected by ASDs, and among these instruments, which is best and in which circumstances it is best. Different HRQL instruments have different domain structures with some instruments better suited to capture the decrement of HRQL outcomes than other instruments. We expect to see more research on testing the sensitivity of different HRQL instruments (both general HRQL and preference-based HRQL instruments) in this special population in order to provide more evidence to select appropriate instruments to evaluate the value of services or interventions for children with ASDs. Our ongoing research that compares generic instruments in this population found that the choice of generic instrument used to measure preference-weighted scores can have a substantial influence on estimated QALYs gained for both the child [109] and the caregiver

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[117]. Clinical measurement tools used to evaluate improvement from interventions or services also need to be tested in order to provide information regarding the magnitude of changes in HRQL and preference-based HRQL outcomes.

Pharmacoeconomic and outcomes researchers have the potential to contribute greatly to the field of autism through research describing clinical, health services and cost–effectiveness applications. We hope and expect that this review will encourage researchers to invest into this important and challenging field.

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Key issues

- Measuring health outcomes in children with autism spectrum disorders (ASDs) presents methodological challenges related to variability of child development, cognitive disability and communication deficits.
- Several instruments may be useful to capture and measure health outcomes in children with ASDs in response to interventions or services received.
- Variation in clinical and behavioral measures can be used as anchors to monitor the sensitivity of health-related quality of life (HRQL) outcome measures including preference-based measures for economic analysis.
- There is limited information to show how different clinical or behavioral measures are associated with HRQL and preference-based HRQL outcomes.
- Little is known about the relative value of additional spending for children with ASDs.
- No study has examined cost–effectiveness of ASD-related services using guidelines developed by the US Panel on Cost–Effectiveness.
- Owing to the burden of ASDs on families, economic evaluations of interventions and treatments for children with ASDs should account for impacts on the family.

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Table 1

Relevance of the domain characteristics included in pediatric health-related quality-of-life instruments to autism spectrum disorder symptoms.

Domains	Core impairments			Associated behaviors						
	Social interaction	Language as used in social communication	Symbolic or imaginative play	Hyperactivity/inactivity	Aggression	Self-injury	Anxiety	Emotional liability	Obsessive–compulsive-like	Sleep
PedsQL 4.0										
Physical health				X						
Psychosocial health		X						X		
Emotional functioning							X			X
Social functioning	X	X		X	X					
School functioning	X	X								
CHQ										
Physical functioning				X						
Social functioning	X	X								
Bodily/discomfort										
General behavior	X		X	X	X	X			X	
Mental health							X	X		
General health perception										
Self esteem										
Parental impact	X	X	X							
Family functioning	X	X	X							
HSQ										
Physical health				X						
Mental health			X				X	X		
Social relations	X	X								

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Domains	Core impairments			Associated behaviors						
	Social interaction	Language as used in social communication	Symbolic or imaginative play	Hyperactivity/inactivity	Aggression	Self-injury	Anxiety	Emotional liability	Obsessive–compulsive-like	Sleep
General health										
Satisfaction with development	X	X								
CHIP-CE										
Satisfaction (with self and health)										
Comfort (emotional and physical symptoms and limitation)							X	X		
Resilience (positive activity that promotes health)										
Risk avoidance (risky behaviors that influence future health)						X				
Achievement (of social expectations in school and with peers)	X	X								
FS II-R										
Communication	X	X								
Mobility										
Mood							X	X		
Energy			X	X						
Play	X		X	X	X	X			X	
Sleep										X
Eating										
Toilet patterns										
KIDSCREEN-27										
Physical				X						
Psychological							X	X		
Autonomy and parent relationship	X									

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Domains	Core impairments			Associated behaviors						
	Social interaction	Language as used in social communication	Symbolic or imaginative play	Hyperactivity/inactivity	Aggression	Self-injury	Anxiety	Emotional liability	Obsessive–compulsive-like	Sleep
Peers and social support										
School environment	X	X								

CHIP-CE: The Child Health and Illness Profile – Child Edition; CHQ: The Child Health Questionnaire; FS II-R: The Functional Status II-R; HSQ: The Health Status Questionnaire; PedsQL: The Pediatric Quality of Life Inventory.

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Table 2

Relevance of the domain characteristics included in preference-based health-related quality-of-life instruments to autism spectrum disorder symptoms.

Domains	Core impairments			Associated behaviors						
	Social interaction	Language as used in social communication	Symbolic or imaginative play	Hyperactivity/inactivity	Aggression	Self-injury	Anxiety	Emotional liability	Obsessive–compulsive-like	Sleep
EQ-5D-Y										
Mobility										
Self-care										
Usual activity	X		X						X	
Pain/discomfort										
Anxiety/depression							X	X		
SF-6D										
Physical functioning				X						
Role limitation										
Social functioning	X	X								
Pain										
Mental health							X	X		
Vitality				X						
HUI3										
Vision										
Speech	X	X								
Ambulation				X						

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Domains	Core impairments			Associated behaviors						
	Social interaction	Language as used in social communication	Symbolic or imaginative play	Hyperactivity/inactivity	Aggression	Self-injury	Anxiety	Emotional liability	Obsessive–compulsive-like	Sleep
Dexterity										
Emotion							X	X		
Cognition		X								
HUI2										
Sensation										
Mobility										
Emotion							X	X		
Cognitive		X								
Self-care										
Pain										
Fertility										
AQoL-6D										
Independent living										
Relationships	X	X								
Mental health							X	X		
Coping										
Pain										
Senses										
CHU9D										

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Domains	Core impairments			Associated behaviors						
	Social interaction	Language as used in social communication	Symbolic or imaginative play	Hyperactivity/inactivity	Aggression	Self-injury	Anxiety	Emotional liability	Obsessive–compulsive-like	Sleep
Worried							X	X		
Sad								X		
Pain										
Tired				X						
Annoyed					X				X	
Schoolwork	X	X								
Sleep										X
Daily routine	X			X					X	
Activities	X			X						

AQoL-6D: The Assessment of Quality of Life Mark 2; CHU9D: The Child Health Utility 9D; EQ-5D-Y: The EuroQol five-dimension questionnaire (youth version); HUI: The Health Utilities Index; SF-6D: The 6-Dimension Short Form.