New York State Clinical Practice Guideline on Assessment and Intervention Services for Young Children (Ages 0-3) with Autism Spectrum Disorders: Update – 2017

REPORT OF THE RESEARCH OF EVIDENCE

New York State Department of Health

Bureau of Early Intervention

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Contents

Introduction

To inform the work of the consensus panel convened to update the New York State Clinical Practice Guideline on Assessment and Intervention Services for Young Children with Autism/Pervasive Developmental Disorders (Autism Spectrum Disorder(ASD)) (referred to as NYSDOH ASD Guideline throughout this report), literature reviews were undertaken by clinical/researchers with expertise in specific areas. These experts were responsible for identifying and reviewing peer-reviewed, published scientific studies applicable to young children ages birth to three years of age in the areas of screening and diagnostic assessments for young children with possible ASD; and, birth through five years of age for intervention methods, health assessments, and medical interventions and treatments.

These exhaustive reviews were intended to provide members of the consensus panel with a current view of the status of the evidence to assist the panel in their work to update the CPG. In addition, the systematic review of therapies for children with ASD, ages birth to 12 years of age, behavioral interventions for children 0-12 years of age prepared by the Vanderbilt Evidence-based Practice Center for the Agency for Healthcare Quality Review (AHRQ) (Weitlauf et al. 2014), was made available to the panel. In total, six topic-focused literature reviews were conducted by expert reviewers for use by the panel, encompassing the following areas: (1) ASD screening instruments; (2) ASD diagnostic instruments; (3) health/medical assessments and interventions; (4) behavioral and educational interventions, through 2011; (5) parent-mediated interventions; and, (6) interventions for children published in peer-reviewed studies after the AHRQ review (Weitlauf et al, 2014).

Evidence-based review procedures have evolved significantly and developed into more formal procedures (e.g., numerical ratings for research quality, inter-rater reliability checks) since the 1999 NYSDOH ASD Guideline was developed. For the current update, a mixed-methods review strategy was used by the expert reviewers, with a more formal evidence-based approach to literature review and study abstraction, and a systematic review approach (Grant & Booth, 2009) for research quality assessment, synthesis, and conclusions. The literature reviews across the clinical recommendation areas (screening, assessment, and intervention) were rendered consistent by specifying search terms, data bases searched, clear inclusion criteria, abstract review and article selection by a senior autism researcher, and detailed chart abstraction based on parameters detailed by a methodologist.

This *Report of the Research* presents the work completed by expert reviewers to support the panel's deliberations. It is important to note that panel members did not participate in the review of the literature used as evidence to update the CPG. Instead, the panel used the work of expert reviewers (most of whom were also panel members) to inform their recommendations.

Screening for Autism Spectrum Disorders in Young Children

Published Research Evaluating Early Screening Instruments for Autism: Years 1999-2014

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A. Screening for Autism Spectrum Disorders in Young Children: Methods and Results of Updated Literature Review and Appraisal for Screening Instruments.

A.1 Literature search

A systematic literature search was conducted through the New York Medical College library. The databases searched included Medline, PubMed, PsycInfo, and ERIC. Once an autism screening instrument was identified as within the appropriate age range, a search was performed using the instrument's name as the search term in order to identify potential articles fitting the inclusion criteria. Finally, reference lists of included articles were reviewed for the same purpose.

A.2 Selecting articles for review

The computer-based literature search yielded 2,188 abstracts. All the abstracts were reviewed by the Principal Investigator (PI) for this part of the literature review and full articles were obtained for those that appeared potentially relevant (N=52). All articles pulled for detailed review were screened and a subset was then selected for more in-depth review if they met the inclusion criteria that for the 1999 NYSDOH ASD Guideline update, which were as follows:

Table A-1
CRITERIA FOR SELECTING STUDIES FOR IN-DEPTH REVIEW

- Be published in English in a peer-reviewed scientific/academic publication
- Provide original data about efficacy of an assessment method for autism spectrum disorder
- Evaluate an assessment method currently available to providers in the U.S.
- Provide an adequate description of the assessment methods evaluated, or provide a reference where such a description could be found
- Evaluate subjects of appropriate age, that is, primarily children under three years of age
- Compare the findings of the test to an adequate reference standard**
- Conduct a Receiver Operator Characteristics (ROC) analysis, that is, report the sensitivity and specificity or positive predictive value of the test compared to an adequate reference standard OR provide enough data so that these can be evaluated.
- Provide evidence for the instrument's efficacy based on an ROC analysis

** The clinical judgment of an experienced, qualified professional using DSM-IV-TR or DSM-5 was considered adequate, although the majority of articles also use the ADOS and other standardized instruments.

As the studies were reviewed using the QUADAS-2 probe questions (see page 27), more bases for exclusion were considered. In some past studies, the screening tools were applied as part of a program of screening and as a result, a "clear path" could not be traced from the instrument's initial passes/fails to later diagnostic status. Table A-2 shows the final selection of screening instruments and associated studies that were reviewed in depth as part of the evidence base. Table A-3 presents those instruments that were excluded and why. There are ten instruments mentioned in Table A-3 that were not included because of basic exclusion criteria but may be well-known as screening instruments and appear in other reviews. It was felt that the reader would benefit from knowing the evidence base status for them.

Table A-2: Instruments and Associated Articles Reviewed
CSBS-DP* ITC: Infant Toddler Checklist: ITC ***Communication and Symbolic Behavior Scales-Developmental Profile**
Pierce, K., Carter, C., Weinfeld, M., Desmond, J., Hazin, R., Bjork, R., & Gallagher, N. (2011)
*Wetherby, A.M., Woods, J., Allen, L. Clear, J., Dickinson, H. & Lord, C. (2004)***
*Wetherby, A. M., Brosnan-Maddox, S., Peace, V., & Newton, L. (2008)***
***Discussed but not considered an ROC article for final review*
Modified Checklist for Autism-Revised, with Follow-up Interview; M-CHAT- R/F
Robins, D.L., Casagrande, K., Barton, M., Chen, C.A., Dumont-Mathieu, T., & Fein, D. (2014)
Parent Observation of Social Interaction: POSI
Smith, N. J., Sheldrick, R. C., & Perrin, E., (2013)
Parent Observation of Early Milestones: POEMS
M. A. Feldman, R. A. Ward, D. Savona et al. (2012)
Screening Test for Autism in Two-Year-Olds: STAT
Stone, W. L., Coonrod, E. E., & Ousley, O.Y. (2000)
Turner, L. M., &. Pozdol, S.L. (2004)
Stone, W. L., McMahon, C. R., Yoder, P. J., & Walden, T.A. (2008)
Autism Detection in early Childhood: ADEC
Nah, Y. H., Young, R. L., Brewer, N., & Berlingeri, G. (2014)
Hedley, D. Nevill, R. E., Monroy-Moreno, Y. et al. (2015)

Table A-3: Level 1 Screening Instruments Not Reviewed

Name, Author	Ages Targeted and Administration Type	Reasons for Exclusion
Pervasive Developmental Disorder Screening Test-II (PDDST-II,) Siegel, 2004	12-48 months, Parent/caregiver checklist (three levels of screener)	• No published ROC studies
First Year Inventory Watson, Baranek, Crais, Reznick, Dykstra, &Perryman, 2007; Turner-Brown, Baranek, Reznick, Watson, & Crais, 2013	12-month-olds Parent/caregiver checklist	• Being revised • Published research does not have adequate ROC evidence.
Early Screen for ASD Traits (ESAT) Dietz, Swinkels, van Daalen, Engeland, & Buitelaar, 2006; Swinkels, Dietz, van Daalen, Kerkof, van Engeland, & Buitelaar, 2006	14-15 months Parent/caregiver checklist	• Developed in Europe, no English translation • Published research reports on a several – stage screening program rather than on the ESAT itself, so ROC does not represent the screener
Checklist for Early Signs of Developmental Disorders (CESDD) Dereu, Warreyn, Raymaekers et al., 2010	3 to 36 months Daycare staff checklist	• Developed in Europe, no English translation • Published research reports on a several – stage screening program rather than on the CESDD itself, so ROC does not represent the screener
Quantitative Checklist for ASD in toddlers -10 (Q-CHAT-10)	15 – 47 months Parent/caregiver checklist	• Included older children and did not analyze < 3 or < 2 year olds separately* • No U.S. sample

Table A-3: Level 1 Screening Instruments Not Reviewed		
Name, Author	**Ages Targeted and Administration Type**	**Reasons for Exclusion**
Allison, Baron-Cohen, Wheelwright, Charman, Richer, Pasco, & Brayne, 2008		
*An important finding of the evidence-based review was that strong reliability and validity was more difficult for children under 18 months of age. As children approached three years old, prediction was much stronger. When children even older than three years old are included, the ROC results may not represent children 12-24 month when screened.		

Table A-4: Level 2 Screening Instruments Not Reviewed		
Name, Author	**Ages Targeted and Administration Type**	**Reasons for Exclusion**
ASD Observation Scale for Infants (AOSI) Bryson, Zwaigenbaum, et al., 2008 Zwaigenbaum, Bryson, & Garon, 2013	6 – 18 months Clinician observation instrument	• Earlier studies were promising but most recent study showed inadequate Se and Sp for clinical use
Social Communication Questionnaire (SCQ) Rutter, M., Bailey, A., & Lord, C., 2003	Originally for 4 years+ but tested with children 2 – 4 years Parent/caregiver checklist	• Research results suggest that the SCQ does not predict ASD for children under 3 yo
Developmental Behavioural Checklist- Preschool (DBC-P) Gray & Tonge, 2005 *Developmental Behavioural Checklist-Early Screen (DBC-ES)* Gray & Tonge, 2008	18-48 months 20-51 months Parent/caregiver checklist	• Included mostly older children and did not analyze younger children separately* • Non-US sample
Visual Impairment and Social Communication Schedule (VISS) Absoud, Parr, Salt, & Dale, 2011	21 months – 7 years of age Clinician observation instrument	• Included mostly older children and did not analyze younger children separately* • Non-US sample
Screen for Social Interaction -Younger (SSI-Y) Ghuman, Leone, Lecavalier, & Landa, 2011	24 – 42 months Parent/caregiver checklist	• Out of age range: although range was 24 – 42 m, M was 34.1 m
*An important finding of the systematic review was that strong reliability and validity was more difficult for children under 18 months of age. As children approached three years old, prediction was much stronger. When children even older than three years old are included, the ROC results probably do not represent children 12-24 month when screened.		

A.3 Considerations for the Review of Evidence

Features of Studies Testing the Predictive Validity of an ASD Screening Instrument. Studies are conducted differently depending on whether the instrument is intended to be a Level 1 (population level) or Level 2 (for high-risk children) screener. How this affects the recruitment, inclusion criteria, and number of participants is covered in the sections below. However, every study compares the screening results to a reference standard or "gold standard," which consensus dictates to be the true test of whether the child has the condition or not. For autism spectrum disorder, this invariably entails a "best estimate diagnosis" by an experienced practitioner who is drawing from a variety of information gathered about the child (e.g., history, caregiver interview, standardized tests, and direct observation of the child).

When a child fails a screening test, he/she is considered at increased risk for the condition, and the result is called positive. When the child passes the screener, the result is called negative; the child is not considered at increased risk for the condition. The screener results, characterized as positive or negative, are then compared to the reference standard, which is also determined as positive or negative for each child. When a child is positive for the condition on the screener and is shown to have the condition on the reference standard (the "best diagnosis"), then it counts as a true positive. If the child did not receive the diagnosis on the reference standard, then the screening result counts as a false positive. If the child is negative for the screener on the condition, and does not receive the diagnosis on the reference standard, the screening result counts as a true negative. If the child is negative for the screener and is diagnosed with ASD on the reference standard, the screening result counts as a false negative.

Sensitivity (Se) and specificity (Sp) are calculated with proportional formulae using true and false positives and negatives. In explanatory terms, Se represents the degree to which the screener accurately detects the condition. The measure runs from 0 to 1.0, with 1.0 being perfect detection. However, the predictive validity of the screener is only understood by considering both Se and Sp together. Sensitivity can be very high if the screener has included almost everybody, and in doing so, of course, it included children with ASD, along with children didn't have ASD. Therefore, Sp balances out the Se by showing that it did not include too many children who in fact had a different developmental disorder or had no developmental problems at all.

Acceptable levels of Se and Sp depend on the outcome or condition of interest. More specifically, for the detection of a preventable communicable disease, investigators may tolerate lower specificity (greater percentage of false positives) for higher sensitivity (greater percentage of true positives). Nevertheless, it is suggested that the threshold values for acceptable levels of sensitivity and specificity should be at least .80 or greater, although accuracy levels of .90 or above are considered optimal (Glascoe, 1991; Plante & Vance, 1994).

Positive Predictive Value (PPV) is a measure that reflects the percentage of children who screened positive and who did have the condition based on the gold standard testing. Negative Predictive Value (NPV) is the inverse—the percentage of children who screened negative and who did not have the condition. Positive and negative predictive values are directly related to the prevalence of the condition under study within the population; these measures are not intrinsic to the instrument. In other words, a screening instrument that has high sensitivity and specificity may have low PPV if the prevalence of the condition is low—a positive result is less likely to be accurate if a condition is rare.

The ideal procedure for examining the predictive validity of a screening instrument involves a direct route between screener administration and diagnostic outcomes, with the most knowledge available about scoring outcomes for every child who was given the screener. This can be challenged by attrition during the various phases of the study, and studies may include additional steps and criteria for a child to advance from one phase of screening and testing to the next.

Types of Screeners (Administration). ASD screening tools (or any type of behavioral screener) generally take two forms: a caregiver-rated checklist or a clinician observation. One variant is to have the clinician administer the checklist to the parent.

A.4 Screening Instrument Reviews

For this review, each screening instrument was described and then critiqued in the following way. The extant literature on the instrument was examined including studies on the instrument's development, how it is administered and scored, and how the constructs it measures are described. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (Whiting, Rutjes, Westwood, et al., 2011) was adapted in the following way: (1) the four domains of Participants, Index Test (the screening tool), the Reference Standard (the "gold standard"), and Timing and Flow were used as units of review with the additional domains of Evaluation and Performance; (2) probe questions were developed for each of the domains; and, (3) the probe questions were applied to each study and conclusions were summarized.

Table A-5 shows the probe questions developed for this review and their significance.

Table A-5: Research Probe Questions for Early ASD Screening Instruments

DOMAIN	PROBE QUESTIONS	SIGNIFICANCE
Participants	**Level 1**	
	Was the sample appropriate in size and scope?	A large population-based sample is needed for accurate ROC investigation. High-risk children and those with established diagnoses are often used when developing the instrument, however.
	How representative were the children and families in terms of demographics?	Enables generalizability.
	Level 2	
	Was the sample appropriate in size and scope?	Referred to clinic, high-risk due to having an older sib diagnosed with ASD, other.
	Did they use a sample matched for developmental level?	When discriminating ASD from DD, some screener items may be associated with lower developmental level rather than specific to ASD since the ASD samples tend to have lower developmental attainments than all other groups.
Screening Instrument	Was there anything about how the screener was administered that would differ from its intended use in a non-research, community setting?	Examples: extensive training given to providers, research assistants collecting data, items being part of a larger questionnaire, parents being sensitized to ASD symptoms.
Reference Standard	Did all children receive a Best Estimate Diagnosis (BED) from in-person evaluations? How extensive was the information available to the clinician making the BED?	(Some studies used diagnoses resulting from community-based clinicians.) How "gold" the gold standard is can vary along a continuum. The gold standard appears to be Best Estimate Clinical Diagnosis, but informed by the ADOS and possibly the ADI-R plus other disciplinary evaluations.
	Were the reference standard evaluators blind to the screener risk status of the children?	Bias could occur if the evaluators were aware of the screening results.
	What diagnostic outcome categories were used to test prediction from screener to reference standard?	The most informative comparisons include ASD and other DDs and TD children. Studies varied in how different severity levels of ASD were included for prediction.

Table A-5: Research Probe Questions for Early ASD Screening Instruments		
DOMAIN	**PROBE QUESTIONS**	**SIGNIFICANCE**
	How were different severity presentations of ASD addressed?	
Timing and Flow	Was there excessive attrition through any phase of screening and evaluation?	If so, it would be important to know if some systematic source of attrition could lead to bias.
	Were there conditions besides attrition that filtered the negative and positive screens from the original screening to the reference standard diagnostic testing phase?	This would include other screening tests and procedures, or, for example, physicians referring for evaluation even if screen was negative.
Calculating ROC coefficients	Was the calculation of sensitivity and specificity supported by available data?	E.g., if false negatives and positives from original screening cannot be followed up, then true Se and Sp cannot be known.
	Were separate calculations made for the younger children?	The youngest children (12-14 months and below) pose the greatest challenge to measurement and prediction.
What was the predictive performance of this test?	ROC characteristics	Se, Sp, PPV, NPV
	Developmental level of children who were true positives?	This will help to compare screening tests in terms of which children are being detected (more or less delayed).
	Percent of false positives with other developmental delays?	If a large proportion of false positives have other disabilities or delays besides ASD, this is important information about the screener's utility.
ROC=receiver operator characteristics; ASD=autism spectrum disorder; DD=developmental disabilities; BED=best estimate diagnosis; ADOS=autism diagnostic observation schedule; ADI-R=autism diagnostic interview-revised; TD=typically developing; Se=sensitivity; Sp=specificity; PPV=positive predictive value; NPV=negative predictive value		

For the Participants domain, different questions are needed for Level 1 vs. Level 2 instruments. The differential parameters are discussed more in depth in the Results section. For the Screening Instrument domain, it is important to note if there is anything about how the instrument was administered in the study that would differ from how it would be used in the community. Examples are provided in the table and in the results.

For the Reference Standard domain, the extent to which the participants each had face-to-face evaluations with Best Estimate Diagnosis, as well as how this was supported by standardized procedures and other disciplinary evaluations, was noted. (N.B., as part of the inclusion criteria, only studies with Best Estimate Diagnosis based on DSM-IV or DSM-IV-TR criteria were included.) A second very important question was whether or not those who conducted the diagnostic evaluations were blind to the screener status of the children, i.e., if they were screen negative or positive, since expectation bias could be introduced in this way. Finally, it was important to note what outcome categories the study considered, so that information about ASD severity level of children and differentiation from other types of disabilities could be known.

The Timing and Flow domain has several features. Two important questions—was the screener done prospectively and was the time interval between the screening and diagnosis adequate—were not included because conditions were met for all studies reviewed. The probe question used refers to conditions moving children from screening to diagnosis that could obscure interpretation directly from the screening tool being examined. It was this probe question that led to understanding that a number of the studies had multi-step

screening protocols without sufficient analysis of Se and Sp for each step, and therefore such studies were eliminated from the more in-depth critique.

In addition, two other probe questions were used to evaluate the results *per se* of the instrument. The first was what developmental characteristics of the children identified as having ASD were presented. This will allow a comparison across screeners for which children were detected in terms of overall developmental level. The second referred to what extent the false positives were detected other types of disabilities.

A.5 Results of Research Reviews of Level 1 Instruments

Table A-6 summarizes the methods and findings for the screening instrument studies reviewed. Table A-7 shows the results from applying the research probe questions.

Table A-6: Research Summary for Level 1 Autism-Specific Screening Instruments

Screener	Ages in Months	Adminis-tration	Article	Se, Sp, PPV	Research Summary
Level 1 Screening Instruments					
ITC	8-24	Parent-rated checklist	Pierce, Carter, Weinfeld et al., 2011 Goal: To determine the feasibility of implementing the ITC at the 1-year check-up to detect cases of autism spectrum disorders (ASD), language delay (LD), and developmental delay (DD).	The ITC was found to function best as a broadband screener, with 138 out of 10,479 toddlers found to have developmental delays, including 32 children with ASD. The PPV for all delays was .75.	Study tested the ITC as an autism screener when given to parents through pediatric practices at the one-year well child checkup. Pediatricians (n = 137) with practices across 30 different offices participated. 10,479 infants who went for a 1-year check-up were screened.

Table A-6: Research Summary for Level 1 Autism-Specific Screening Instruments					
Screener	**Ages in Months**	**Adminis-tration**	**Article**	**Se, Sp, PPV**	**Research Summary**
Level 1 Screening Instruments					
M-CHAT-R/F	18-30	Parent–rated checklist	Robins et al., 2014 Goal: To validate the MCHAT-R/F and demonstrate greater effectiveness over the original MCHAT.	Rate of detection was 67 per 10,000. Total of 3 was when Se and Sp exceeded 0.90. Se = .91 Sp = .95 Totl3 w F/U Totl 3 : Se=.67 Sp=.99* PPV=.51 NPV=.99 Totl3 w F/U Totl 2 : Sens=.85 Spec=.99* PPV=.47 NPV=.99 This was calculated "assuming that all negatives were true negatives…." In this case only PPV can be known.	Large population based sample (N=16,071). Parents of toddlers presenting for 18- and 24-month well-child care visits filled out the M-CHAT-R. Out of 16,071 screened, there were 1,155 positives (7.2 %). Parents who had filled out a positive-scoring M-CHAT-R were invited to participate in the Follow-Up Interview, yielding 82% of the positive screens (946 out of 1,155). This second level of screening eliminated 598 or 63%. Out of the still-positive children, n=348, they were able to evaluate 221, or 63%. Out of them, 105 (47%) were found to have ASD using a gold standard evaluation and 116 did not. Best estimate dx by evaluators blind to screener status.
POSI	18-35	Parent-rated checklist	Smith, Sheldrick, & Perrin, 2013 Goal: to investigate the internal reliability and concurrent validity of a new, abbreviated screening instrument for	In Study 1, for 18-30 month olds, Se=.96, Sp =.53. Based on the two studies, the measure had good to excellent sensitivity (.89 – .96), performing better among 18-30-month-old children.	Study 1: Out of a group of n= 217 children (4 excluded due to incomplete data), 137 (63%) received an ASD diagnosis. Separated out for analysis were 18- 48 mos. vs 18 – 30 mos. Although the

Table A-6: Research Summary for Level 1 Autism-Specific Screening Instruments

Screener	Ages in Months	Adminis-tration	Article	Se, Sp, PPV	Research Summary
Level 1 Screening Instruments					
			ASD, the Parent's Observations of Social Interactions (POSI); 2-part study.	Performance measures from Study 2 must also be received with caution given that outcome diagnosis was based on parent report of community diagnoses.	entire sample of 217 ranged from 18 to 48 months, it was not clear how many were in the 18-30-mos. subsample. Study 2 was a validation study. They combined low-risk children from a larger development study with high risk children from clinics and the NICU follow-up.

ITC=Infant-Toddler Checklist; Se=sensitivity; Sp=specificity; POSI= Parent Observation of Social Interaction; ASD=autism spectrum disorder; DD-developmental disabilities; LD=language development; N=large sample; n= moderate sample size; M-CHAT-R/F= Modified Checklist for Autism in Toddlers-Revised; PPV=positive predictive value; NPV=negative predictive value

Table A-7: Level 1 Probe Questions

PROBE QUESTIONS	ITC PIERCE ET AL., 2011	M-CHAT-R/F ROBINS ET AL, 2014	POSI SMITH, SHELDRICK, & PERRIN, 2013	
			STUDY 1	***STUDY 2***
SAMPLE/PARTICIPANTS				
Was the sample appropriate in size and scope?	+/- Yes/No, started with a very large, low-risk community sample n=10,479; but attrition was very high--for the reference standard evaluation phase, n=184, or 4% of high-risk sample. 137 pediatricians in 30 practices in California participated. Final sample examined was: ASD=32-37, LD=56, DD=9,	+ Yes, a very large, low-risk community sample N=16,071; 137 pediatricians in 30 practices in California participated.	+ Yes but for an instrument development study since it was a high-risk sample. N=217.	+ Yes for a development study. Mix of low- and high-risk. N=232.

Table A-7: Level 1 Probe Questions

PROBE QUESTIONS	ITC PIERCE ET AL., 2011	M-CHAT-R/F ROBINS ET AL, 2014	POSI SMITH, SHELDRICK, & PERRIN, 2013	
			STUDY 1	***STUDY 2***
	other DD=36, TD=41.			
How representative was the sample?	- These parameters were not reported.	+/- They reported demographics but did not report how representative they were of the catchment area.	+/- Reported ethnicity, maternal education, and Medicaid status; did not report representivity	+/- Reported but did not compare.
Were there exclusion criteria based on other disabilities?	They specified that no exclusion criteria were exercised for either the population sample or for follow-up.	Previous ASD dx or "medical condition that precluded evaluation."	Exclusion criteria were significant blindness, deafness, or severe physical disability.	Not reported
Did investigators use sub-samples matched for developmental level?	N/A	N/A	No	No
SCREENING INSTRUMENT				
Was there anything about how the screener was administered that would be different from its intended use in a non-research, community setting?	+ No	- Yes. Pediatricians did not score, research assistants collected them and scored them. Research assistants also administered the follow-up interview.	- Yes. The POSI and M-CHAT questions were embedded in a longer questionnaire so it is not known how the POSI given alone would perform.	- Yes. The POSI and M-CHAT questions were embedded in a longer questionnaire so it is not known how the POSI given alone would perform.
Were there any issues regarding the way it is scored in the study?	Note that the ITC can be failed in four different ways—low score on either or both of two subscales, total score; there may be differences in true and false positives given the source of fail criterion. In addition, a child would be considered high-risk if the parent checked off a box	Note that the M-CHAT-R was failed both by exceeding a cut- off score, as well as a pediatrician checking a concern box.	No	No

Table A-7: Level 1 Probe Questions

PROBE QUESTIONS	ITC PIERCE ET AL., 2011	M-CHAT-R/F ROBINS ET AL, 2014	POSI SMITH, SHELDRICK, & PERRIN, 2013	
			STUDY 1	***STUDY 2***
	about having concerns regardless of other scores.			
REFERENCE STANDARD				
Did all children receive a BED from in-person evaluations? How extensive was the information available to the clinician making the Best Estimate Diagnosis?	+ Yes Cognitive, ADOS-T, and ADI-R; children seen every 6 months up to three years of age. They evaluated every 6 months and gave "at-risk" dx's of ASD 12 – 18 months, "provisional" dx's from 19 – 31 months and established dx's 32 – 36 months with ADI-R. Five children with provisional dx's no longer had a dx by the last evaluation.	+ Yes, Cognitive, ADOS, CARS, Vineland.	+/- Yes, by developmental pediatricians with all info available to them; testing results could include ADOS, CARS, cognitive, but it wasn't specified how much each was used throughout the sample.	- No. Parents reported community dx.
Were the reference standard evaluators blind to the screener risk status of the children?	- Not Reported	+ Yes	+/- They had access to all items answered on the POSI and used it qualitatively along with all other information but did not know the scores per se.	+ Yes.

Table A-7: Level 1 Probe Questions

PROBE QUESTIONS	ITC PIERCE ET AL., 2011	M-CHAT-R/F ROBINS ET AL, 2014	POSI SMITH, SHELDRICK, & PERRIN, 2013	
			STUDY 1	***STUDY 2***
			("incorporation bias")	
What diagnostic outcome categories were used to test prediction from screener to reference standard?	+ ASD, LD, DD, and no diagnosis. LD and DD defined by Mullen Scores, "other" by parameters such as motor delay.	ASD vs non-ASD for purposes of ROC. Other diagnoses were discussed such as language delay and global delay but no analyses presented.	ASD or not.	ASD or not.
TIMING AND FLOW				
Was there excessive attrition through any phase of screening and evaluation?	-Yes. Out of 10,479, there were 1316 fails. Out of those, only 346 were referred for testing by the researchers, with a list of practical reasons why the others might have been missed. Out of 346 they lost another 232 for a variety of reasons, so in the end they worked with 184 high risk children plus 41 TD children as a comparison group.	+ No	+ No.	+ No.
Were there conditions besides attrition that filtered the negative and positive screens from the original screening to the reference standard diagnostic testing phase?	Not obviously	No	No	No
EVALUATION				
How were performance/predictive values calculated?	They combined ASD with other DDs to calculate PPV because they were considering	- ASD vs. non-ASD. Problem with calculated Se and Sp based on presumed false	ASD vs. non-ASD	ASD vs. non-ASD

Table A-7: Level 1 Probe Questions

PROBE QUESTIONS	ITC PIERCE ET AL., 2011	M-CHAT-R/F ROBINS ET AL, 2014	POSI SMITH, SHELDRICK, & PERRIN, 2013	
			STUDY 1	***STUDY 2***
	the ITC a broadband screener.	negatives rather than a true count.		
Was performance/prediction for younger versus older children explored?	Screened at 12-15 months But their breakdown showed that *outcome diagnosis* was less stable at 12 – 18 months and became more stable toward 24 months.	No	Yes	N/A all were 16 – 30 mos
PERFORMANCE				
What were the performance/predictive values?	PPV = .75 for all disabilities PPV = .20 ASD alone	PPV <u>Totl3 w F/U Totl 2</u>: .51 PPV <u>Totl3 w F/U Totl 3</u>: .47	<u>18 – 48 mos:</u> Se =.89 Sp = .54 <u>18 – 30 mos only:</u> Se - .96 Sp= .53	Se = .74 Sp = .84
What was the developmental level of children detected?	IQs ranged widely but did include higher functioning children: MSEL Composite M = 78.6 SD = 17.5 Range = 49 – 106	Reported means and SDs Mullen VR M=29.64 (10.86)	Not reported.	Not reported.
Of the false positives for ASD, what proportion had other developmental or learning disabilities?	69.7%	Did not report		49%.

ITC=Infant-Toddler Checklist; M-CHAT-R/F= Modified Checklist for Autism in Toddlers-Revised ; Se=sensitivity; Sp=specificity; PPV=positive predictive value; NPV=negative predictive value; BED=best estimate diagnosis; MSEL=Mullen Scales for Early Learning; ASD=autism spectrum disorder; N=large sample; n= moderate sample size; DD-developmental disabilities; LD=language development ; TD=typically developing; POSI= Parent Observation of Social Interaction; ADOS-T=autism diagnostic observation schedule; ADI-R=autism diagnostic interview-revised; dx=diagnosis; CARS= Childhood Autism Rating Scale; MSEL=Mullen scales of early learning; SD=standard deviation; M=mean; VR= Visual Reception;

Conclusions regarding the research evidence are as follows:

Infant-Toddler Checklist (ITC)

The ITC is a short parent checklist that can be applied in community settings, and has the distinction of targeting very young children—8 to 24 months of age. It was developed as a measure to detect language delay and disability during the first two years, but given its focus on social communication, it has been investigated as an autism screening instrument. Wetherby and colleagues (2004, 2008) reported its performance as part of a program of screening and concluded that it functioned best as a broadband screener, accurately detecting children as young as 9 months with a variety of developmental delays, including those with ASD. In spite of the important information these studies provide, they were limited because of the several phases of screening the children underwent that then prevented interpretation of the ITC scores alone as predictors. As a result, Pierce et al. (2011) is the one ROC study that met the inclusion criteria for the current project.

These authors made an impressive attempt to complete a population-based study, which is the "true test" for a Level 1 screener, by screening over 10,000 children at approximately 12 months of age. Because of privacy constraints, the researchers could not contact positive screens directly and needed to rely on staff at busy pediatric practices to refer, check the appropriate boxes, and photocopy the paper checklist. As a result, there was excessive attrition. Results showed that, similar to the Wetherby el al. studies, the 12-month screenings functioned best as a broadband screener with a PPV of later diagnosed disability (including ASD) of .75. For ASD alone, the PPV was .20, which is notable given that it was such an early age for social-communication screening. As a group of studies, it was shown that prediction for ASD improves from 9 months to 12 months, and improves even more at 18 months.

The strengths of the study were: A large, low-risk community sample, a well-supported BED at different ages, and well-differentiated outcome groups. The weaknesses were: large attrition, lack of reporting of demographics, lack of distinction between which type of "fails" (i.e., different subscales vs. parent checking off a "concern" box) predicted outcome; lack of reporting whether standard reference evaluators were blind to screening status.

The ITC is recommended for use as a Level 1 (broadband) screener, but additional research is needed on its utility as a Level 2 screener. However, because enough evidence has accumulated to support its use as a broad-band screener that will also detect children with ASD, at younger ages than other instruments, and because of its feasibility (ease of use, time involved, no follow-up interview), it has a number of strengths.

Modified Checklist for Autism in Toddlers-Revised with Follow-up Interview (M-CHAT-R/F)

The M-CHAT-R/F is a Level 1, short, parent-rated checklist also meant for community settings, but with a later age range than the ITC (from 16 to 30 months). The M-CHAT-R/F is the most recent iteration of the most well-known ASD screener, the M-CHAT (Robins et al., 2001). The M-CHAT-R/F has been reported upon in a single 2014 publication (Robins et al., 2014). The Follow-Up Interview must be used to significantly reduce the false positives (by 63%). The article demonstrates that the new scoring is an improvement, and introduces the use of levels of risk based on the screening score, suggesting direct referral without the Follow-Up Interview when the score is over 7.

This study was an ambitious population study, and screened over 16,000 children over 85 pediatric practices in Connecticut and Georgia. Parents of toddlers presenting for 18- and 24-month well-child care visits filled out the M-CHAT-R while at the office, but pediatricians did not score them. Research assistants did so. They did, however, check off a box at the top of the form about whether they thought the child was at risk for ASD given their independent assessment (not all physicians did this consistently, however). Out of 16,071 screened, there were 1,155 positives (7.2 %). Parents who had filled out a positive-scoring M-CHAT-R were then contacted by phone for administration of the Follow-Up Interview. The researchers were able to conduct the second part of the screen, the Follow-Up Interview, with 82% of the positive screens (946 out of 1,155). This second level of screening then eliminated 598 or 63%.

Out of the still-positive children, n=348, the researchers were able to evaluate 221, or 63%. Out of these children, 105 (47%) were found to have ASD using a gold standard evaluation; 116 did not receive the diagnosis. Differences in different cut-off scores for the Follow-up Interview were examined. The PPV for two different cut-offs were as follows: PPV Totl3 w F/U Totl 2:.51; PPV Totl3 w F/U Totl 3:.47.

A methodological problem, however, is that the Se and Sp reported is not "true" (this is mentioned in the *limitations* section of the article). It is often the case that in population sampling studies such as this one, it is impossible to follow-up on more than14,000 children with negative screens to determine which are false negatives or true negatives. The authors did follow up a sampling of negative screens, but with the high attrition and given the strategy, it is unlikely that this sampling accurately reflected the entire group of false negatives. In the case of Sp calculation, the authors used a "presumed" number counting all original negatives as true negatives. Upon inspecting the key papers on the M-CHAT, their Se and Sp reporting had similar challenges. It seems that the M-CHAT-R/F will continue to be widely used; however, it is prudent to point out that definitive research has not yet been conducted for this instrument.

The strengths of the study were: it is one of the very few studies that attempted to include a population study, gold standard testing, evaluators blind to screener-determined risk status, and calculation of PPV. The weaknesses were reporting Se and Sp without the true numbers available, and lack of distinction between which type of "fails" (i.e., cut-off score vs. pediatrician checking off a "concern" box).

In terms of evidence-based support, the M-CHAT-R/F brings with it the research legacy of the M-CHAT. This paper does comprise one population-based study that shows that with the Follow-up Interview, about half the children who screen positive will have an ASD diagnosis. Since this is the instrument in widest use in North America and Europe, it is recommended because it has the strongest evidence base available for any ASD screener for infants and toddlers. Nevertheless there are cautions about its use, notably the high rate of false positives and the uncertain Se and Sp.

Parent Observation of Social Interaction (POSI)

The POSI, a short, 7-item parent-rated checklist, was developed recently by researchers (developmental-behavioral pediatricians) in Boston who wanted to develop a screener for community practice that was shorter than the M-CHAT and did not require a follow-up interview. The POSI was developed in the context of a larger study that investigates many aspects of development in young children (see www.swyc.org). There is currently one published paper (2013) that describes, over two studies, its development and preliminary reliability and validity, including ROC statistics. The studies were not population-based studies because the instrument was in its development phase, and thus needed to have enough high-risk children who would then be diagnosed with ASD; this group needs to be large enough to calculate reliable cut-off scores.

In Study 1, the researchers recruited families coming to a diagnostic evaluation clinic because of concerns about their child's development (e.g., a high-risk sample). Parents filled out the POSI at the same time they filled out the rest of the intake paperwork. Children then underwent a comprehensive evaluation and received a diagnosis. Se for 18 – 30 month olds was .96 and Sp was .53.

Study 2 used an archival data set from a larger study about children's development. Children were recruited from a mix of low-risk and high-risk settings. (This is a compromise between trying it as a Level 1 screener and still including enough children who will have ASD to yield meaningful statistics.) As part of this larger study, volunteer parents filled out the POSI along many other questions. As a result, the archival data had both POSI results as well as *parent-reported community diagnoses.* The authors compared it with the MCHAT at the same time and in general it out-performed the MCHAT using fewer items and no follow-up interview (F/U was not used for MCHAT either). Based on the two studies, the measure had good to excellent sensitivity (.89 – .96), performing better among 18-30-month-old children.

The measure has a strong rationale and shows promise from this preliminary report. However, using the QUADAS-2 analysis, there were risks of bias or methodological weaknesses in many of the domains, and it has not been tested on a large, low-risk sample. It is recommended as a promising tool to use. However, further, high quality studies are needed to add to current evidence on this tool.

A.6 Results of Research Reviews of Level 2 Instruments:

Table A-8 summarizes the methods and findings for the screening instrument studies reviewed. Table A-9 shows the results of the research probe questions.

Table A-8: Research Summary for Level 1 Autism-Specific Screening Instruments

Instrument	Ages in Months	Adminis-tration	Article	Se, Sp, PPV	Research Summary
Parent Observations of Early Milestones (POEMS)					
POEMS	3-24	Parent-rated checklist	Feldman Ward et al., 2012 Goal: To evaluate a newly developed parent report instrument to monitor the behavioral development of infants at risk for ASD due to having older affected siblings.	Cut-off score of 70 Mean Se (across all age groups) = .74 and Sp =.87. Se got higher as age progressed over 3, 6, 9, 12, 18, and 24 months. At 12 months, Se = .71 and Sp = .68. At 18 months, Se = .89 and Sp = .65. PPV overall was .21.	Researchers recruited families with an older sibling diagnosed with autism then followed younger, infant siblings with parents filling out the POEMS multiple times, at least a month apart. Participants were recruited through a website. N=239 families before narrowing down. Participants were then divided into two groups: infant siblings who were confirmed to have ASD at age 36 months (n=7) and those who were not (n=63). They relied on parent report of community diagnosis. They were able to give the ADI-R to 3 out of the 9 children with ASD. Predictions were made using ROC analyses, with a cut-off score of 70.
Screening Test for Autism in Two-Year-Olds (STAT)					
STAT	12-36 Months	Clinician-administered	Stone, Coonrod, & Ousley, 2000 Goal: To 1) examine the validity of the STAT as a Stage 2 screening	Cut off of 2: Se= .83 Sp= .86.	Small sample size of 7 children with autism and 33 with developmental delay (DD) and/or language impairment (LI) (all between 24 and 36 months). BED w/

Table A-8: Research Summary for Level 1 Autism-Specific Screening Instruments					
Instrument	**Ages in Months**	**Adminis-tration**	**Article**	**Se, Sp, PPV**	**Research Summary**
			instrument in a clinic-based sample of 2-year-old children referred for suspected developmental disorders and 2) identify a scoring algorithm for the STAT that would maximize accurate identification of children receiving an independent clinical diagnosis of autism.		cognitive and SPL evals. Evaluators blind to screener status. They were given the STAT while attending a clinic for a full evaluation because of developmental concerns. They developed the scoring and the cutoff scores then applied it to another set of high-risk children.
			Stone, Coonrod, Turner, & Pozdol, 2004 Goal: To derive a scoring algorithm for the STAT using signal detection methods and to examine the reliability and validity of the STAT.	Cut-off score of 2: Se = 92 Sp =.85.	26 children who were diagnosed with autistic disorder were compared to 26 children who were diagnosed with developmental delay and/or language disorder. Best estimate dx w/ cognitive and SPL evals.
			Stone, McMahon, & Henderson, 2008 Goal: To examine the properties of the STAT for children under 24 months.	Adjusted cut-off of 2.75: Se=.95 Sp= 73 PPV =.56	Participants were younger siblings of children dxed with ASD (n=69) and children referred for developmental concerns (n=12). They were administered the STAT from 12 to 24 months and evaluated for ASD at 24 months. Best estimate dx w/ cognitive and ADOS assessments. Evaluators blind to screener status of participants.
Autism Detection in Early Childhood (ADEC)					

Table A-8: Research Summary for Level 1 Autism-Specific Screening Instruments					
Instrument	**Ages in Months**	**Adminis-tration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADEC	12-36 months	Clinician-administered checklist	Nah, Young, Brewer, & Berlingeri, 2014 Goal: To provide a psychometric examination of the Autism Detection in Early Childhood (ADEC), a behavioral assessment tool designed to screen for AD in young children (12-36 months) referred with developmental concerns (Level 2 screening).	At recommended cutoff from manual (11) Se = .94 Sp = .63 At recommended cut-off for "High Risk of ASD" 14, Se = .85 Sp = .79	Recruited children from 12 to 36 months from a variety of sources over a several-year period in order to end up with a varied group of n=70 children diagnosed with AD, PDD-NOS, Other Dev Dis, and Typically Developing. First the research assistants administered the ADEC, then children and parents returned for a full evaluation, using Best Estimate Diagnosis, including the ADOS.
			Hedley, Nevill, et al., 2015 Goal: To assess the psychometric properties of the ADEC in a sample of children who were referred to the child diagnostic and assessment center of a US pediatric hospital due to developmental concerns.	Cutoff score of 1: Se = .94 Sp = .63 A higher cutoff score of 14, associated with the ADEC category of "high risk of ASD:" Se = .85 Sp = .79	Participants were 114 children between the ages of 14 – 36 months referred for diagnostic evaluation. Participants were screened with the ADEC during their first visit. Inclusion criteria for the final sample required that the child had received a diagnostic evaluation from a qualified health professional; or, if only a screening interview had been completed, the child had to be minimally assessed with either the ADOS-2 or the ADI-R and not meet ASD criteria to be included in the No Diagnosis group. Eighteen children were excluded from the study leaving a final sample size of n= 96. The final sample was divided into the following three

Table A-8: Research Summary for Level 1 Autism-Specific Screening Instruments					
Instrument	**Ages in Months**	**Adminis-tration**	**Article**	**Se, Sp, PPV**	**Research Summary**
					groups for further analysis: ASD (n = 48), Developmental Delay (DD; n = 39), and No Diagnosis (ND; n = 10). Clinical personnel participating in the child's standard developmental evaluation were kept blind to ADEC scores. A BED diagnosis of ASD was based on DSM-5 criteria incorporating expert clinical opinion, ADOS-2 results, observation and caregiver interview, and was independent of ADEC scores
POEMS=Parent Observation of Early Milestones; ASD=autism spectrum disorder; Se=sensitivity; Sp=specificity; PPV=positive predictive value; STAT=Screening Test for Autism in Two year olds; N=large sample; n= moderate sample size; ADI-R= autism diagnostic interview-revised; ROC=receiver operator characteristics; DD=developmental delay; LI=language impairment; BED=best estimate diagnosis; SPL= Speech-language Pathologist; ADOS=autism diagnostic observation schedule; ADEC=Autism Detection in Early Childhood; PDD-NOS=pervasive developmental disorder-not otherwise specified; ND=no diagnosis; .					

Table A-9: Level 2 Probe Questions			
PROBE QUESTIONS	**STAT Stone, Coonrod, & Ousley, 2000**	**STAT Stone, Coonrod, Turner, and Pozdol, 2004**	**STAT Stone, McMahon, & Henderson, 2008**
PARTICIPANTS			
Was the sample appropriate in size and scope?	**-** Small*;* ASD=7 and DD/ LI/other Delay=33 for development sample, ASD=12 and DD etc. = 21 for validation sample	- Small; Development and Validation Sample, each: Autistic Disorder, N=13 (T=26) DD or LI, N = 13 (T=26)	- Small; ASD=19 All participants were high risk because of diagnosed older sibling.
Did investigators use a sample matched for developmental level?	+Yes	+ Yes	No
SCREENING INSTRUMENT			
Was there anything about how the screener was administered that	No	No	No

Table A-9: Level 2 Probe Questions			
PROBE QUESTIONS	**STAT Stone, Coonrod, & Ousley, 2000**	**STAT Stone, Coonrod, Turner, and Pozdol, 2004**	**STAT Stone, McMahon, & Henderson, 2008**
would be different from its intended use in a non-research, community setting?			
Were there any issues regarding the way it is scored in the study?	No	No	No
REFERENCE STANDARD			
Did all children receive a BED from in-person evaluations? How extensive was the information available to the clinician making the Best Estimate Diagnosis?	+/- Not clear; ADOS was not used, CARS was reported, and DSM-IV was used as criteria	+/- BED based partially on cognitive and SPL; no ADOS or ADI-R	+ Yes; the information available included ADOS and Mullen
Were the reference standard evaluators blind to the screener risk status of the children?	+ Yes	+ Yes	- Not Reported
What diagnostic outcome categories were used to test prediction from screener to reference standard?	AD vs. DD, LI, and other delays	AD vs. DD and LI.	Autism, PDD-NOS, DD, LI, BAP (Broader Autism Phenotype), and No Diagnosis
TIMING AND FLOW			
Was there excessive attrition through any phase of screening and evaluation?	No	No	No
Were there conditions besides attrition that filtered the negative and positive screens from the original screening to the reference standard diagnostic testing phase?	No	No	No
EVALUATION			
How were performance/ predictive values calculated?	The groups were Autism/Autistic Disorder* vs non-autism, which consisted of developmental delay,	The groups were Autism/Autistic Disorder* vs non-autism, which consisted of developmental delay,	The groups were combined as follows: Autism and PDD-NOS were all ASD; the most false positives were found for 12 – 13 month-olds, so Se and Sp was calculated both with and

Table A-9: Level 2 Probe Questions			
PROBE QUESTIONS	**STAT Stone, Coonrod, & Ousley, 2000**	**STAT Stone, Coonrod, Turner, and Pozdol, 2004**	**STAT Stone, McMahon, & Henderson, 2008**
	language impairment, and other delays. *Leaving out milder children will increase Se and Sp	language impairment, and other delays. *Leaving out milder children will increase Se and Sp	without them. They achieved acceptable Se and Sp levels by raising the cut-off score compared to that for the 24 – 36-month-olds.
Was performance/prediction for younger versus older children explored?	No	No	Yes—reported false positives for three different groups between 12 and 24 months. More false positives for the 12 – 13 month group than older children.
PERFORMANCE			
What were the performance/predictive values?	Unmatched sample: Sp =.83, Se = .86, PPV = .77, NPV = .90 Matched sample: Sp = .83, Se = .83	Matched Sample: Cut-off score of 2: Se = 92 Sp =.85	Using a cutoff of 2.75: Se = .95, Sp = .73, PPV = .56, NPV = .97 Excluding the 12 – 13 month-olds: Se = .93, Sp = .83, PPV = .68, NPV = .97
What was the developmental level of children detected?	Range of DA 11 – 39 months, mean 18 mos at CA mean of 32 mos.	CA M= 32 SD = 3.5 MA M = 17 SD = 7.1	The sample included higher functioning children; at mean of 24 months, MSEL Early Learning Composite: M = 93.5, SD = 23.3
Of the false positives for ASD, what proportion had other developmental or learning disabilities?	Not reported	Not reported	50% of false positives had other DD diagnoses.
STAT=Screening Test for Autism in Two year olds; POEMS=Parent Observation of Early Milestones Scale; ADEC=Autism Detection in Early Childhood; ASD=autism spectrum disorder; BED=best estimate diagnosis; ADOS=autism diagnostic observation schedule; ADI-R=autism diagnostic interview-revised; AD=autistic disorder; PDD-NOS=pervasive developmental disorder-not otherwise specified; DD=developmental delay; LI=language impairment; BAP=broader autism phenotype; TD=typically developing; ROC=receiver operator characteristics; Se=sensitivity; Sp=specificity; ODD=other developmental disabilities; PPV=positive predictive value; NPV=negative predictive value; MSEL=Mullen scales of early learning; M=mean; SD=standard deviation			

Table A-9: Level 2 Probe Questions			
PROBE QUESTIONS	**POEMS Feldman Ward et al., 2012**	**ADEC Nah, Young, Brewer, & Berlingeri, 2014**	**ADEC Hedley, Nevill, et al., 2015**
PARTICIPANTS			
Was the sample appropriate in size and scope?	+ N= 108 All participants were high risk because of diagnosed older	+ N=195 Combination of high-risk (referred for evaluation) and typically	+ N=96 ASD: N= 48, other DD: N = 37, and No Dx: N = 10.

Table A-9: Level 2 Probe Questions			
PROBE QUESTIONS	**POEMS Feldman Ward et al., 2012**	**ADEC Nah, Young, Brewer, & Berlingeri, 2014**	**ADEC Hedley, Nevill, et al., 2015**
	sibling.	developing. AD: N = 70, PDD-NOS: N = 24, Other Dev Dis (ODD): N=37, TD: N= 64.	
Did investigators use a sample matched for developmental level?	No	Yes	Yes
SCREENING INSTRUMENT			
Was there anything about how the screener was administered that would be different from its intended use in a non-research, community setting?	The POEMS was filled out by families every three months. Giving the POEMS many times could sensitize parents to ASD behaviors, especially since they would already be so because of their older child with ASD. However, this is consistent with its intended use within this study.	The team administering the screener received hands-on training, whereas the ADEC manual suggests that the evaluator can use the manual and accompanying CD.	The team administering the screener received hands-on training, whereas the ADEC manual suggests that the evaluator can use the manual and accompanying CD.
Were there any issues regarding the way it is scored in the study?	No	No	N**o**
REFERENCE STANDARD			
Did all children receive a BED from in-person evaluations? How extensive was the information available to the clinician making the Best Estimate Diagnosis?	- No direct examination for diagnostic status. They relied on parent report of community diagnosis. They were able to give ADI-R to 3 out of the 9 children with ASD to confirm.	BED with cognitive assessment, ADOS, and ADI-R if AD or PDD-NOS diagnosis considered. "77.5% had an independent confirmatory diagnosis from either two other independent professionals who were recognized by the state's autism association or other medical professionals such as pediatricians and psychologists."	BED with cognitive assessment, and some combination of ADOS-2, ADI-R, CARS, and ASRS.
Were the reference standard evaluators blind to the screener risk status of the children?	+ Most likely, considering they were clinicians in the community who were independent of the study.	Yes	Yes
What diagnostic outcome categories	Only categories were ASD vs. no ASD. This is	For initial analyses, ASD (AD + PDD-NOS), Other	ASD, Other DD, and TD. For this study, there

Table A-9: Level 2 Probe Questions			
PROBE QUESTIONS	**POEMS** **Feldman Ward et al., 2012**	**ADEC** **Nah, Young, Brewer, & Berlingeri, 2014**	**ADEC** **Hedley, Nevill, et al., 2015**
were used to test prediction from screener to reference standard?	a departure from most studies, which also include other DDs. This appeared to be a function of the study methods, which involved using reports the parents obtained from the community.	DD, and TD. However, authors indicated that the ADEC is intended to detect Autistic Disorder, so PDD-NOS was left out for ROC analysis and this suggests that it will detect more severe children on the spectrum.	appeared to be no isolating of only the more severe children (by using AD only).
TIMING AND FLOW			
Was there excessive attrition through any phase of screening and evaluation? *Were there conditions besides attrition that filtered the negative and positive screens from the original screening to the reference standard diagnostic testing phase?*	No	N/A	No
EVALUATION			
How were performance/ predictive values calculated?	Predictive validity was first explored by forming two groups: infant siblings who were confirmed to have ASD at age 36 months (n=9) and those who were not (n=63). They then compared how the POEMS score diverged over the different age levels.	Investigators left the PDD-NOS group out and compared AD to Other Developmental Disabilities (ODD) with and without the TD group. This can inflate performance compared to studies that include milder children.	Investigators now used as ASD group instead of separating AD.
Was performance/prediction for younger versus older children explored?	Yes – see below. The sensitivity got higher as age progressed over 3, 6, 9, 12, 18, and 24 months. Sensitivity reached the acceptable level at 18 months.	Yes, for 12 – 24 vs. 24 – 36 with no differences found. Did not look at the youngest children (under 18 months).	N**o**
PERFORMANCE			
What were the performance/predictive values?	A cut-off score of 70 resulted in a mean sensitivity (across all age groups) of .74 and	Using a cut-off score of 11:	Cutoff score of 11: Se = .94 Sp = .63 A higher cutoff score of 14, associated with the ADEC

Table A-9: Level 2 Probe Questions

PROBE QUESTIONS	POEMS Feldman Ward et al., 2012	ADEC Nah, Young, Brewer, & Berlingeri, 2014		ADEC Hedley, Nevill, et al., 2015
	specificity of .87; PPV overall was .21. At 12 months, Se = .71 and Sp = .68 At 18 months, Se = .89 and Sp = .65			category of "high risk of ASD:" Se = .85, Sp = .79.
		Unmatched AD vs DD Se = 1.0 Sp = .77 AD vs.DD + TD Se = 1.0 Sp = .89	*Matched* AD vs DD Se = 1.0 Sp = .74 AD vs.DD + TD Se = 1.0 Sp = .90	
What was the developmental level of children detected?	Not reported	Nonverbal IQ AD 48.6(10.2) PDD-NOS 70.6 (13.0) Vineland 62.1(7.9) 72.7(7.3)		Nonverbal IQ ASD 65.1 (21.5) Vineland 79 (43.2) MSEL ELC 54.70(12.6)
Of the false positives for ASD, what proportion had other developmental or learning disabilities?	Not reported	10/70 or 14%		Not reported

STAT=Screening Test for Autism in Two year olds; POEMS=Parent Observation of Early Milestones Scale; ADEC=Autism Detection in Early Childhood; ASD=autism spectrum disorder; BED=best estimate diagnosis; ADOS=autism diagnostic observation schedule; ADI-R=autism diagnostic interview-revised; AD=autistic disorder; PDD-NOS=pervasive developmental disorder-not otherwise specified; DD=developmental delay; LI=language impairment; BAP=broader autism phenotype; TD=typically developing; ROC=receiver operator characteristics; Se=sensitivity; Sp=specificity; ODD=other developmental disabilities; PPV=positive predictive value; NPV=negative predictive value; ASRS=Autism Spectrum Rating Scales; MSEL=Mullen scales of early learning; ELC= Early Learning Composite; M=mean; SD=standard deviation

Conclusions regarding the research evidence are as follows:

Screening Test for Autism in Two-Year-Olds (STAT)

The STAT is a clinician-administered, semi-structured interactive screener that shows adequate to strong prediction when used with one–to-three year olds. Three papers with ROC reported comprise the evidence base. The first, Stone, Coonrod, and Ousley (2000), wherein participants were 24-35 months old, had adequate methods with the important exception of a *very small sample size* (children with ASD n=7). For this study, Se=.83 and Sp=.86. The second study had more participants but sample size was still small (N=13 ASD and N=13 comparison group). This study produced Se = .92 and Sp = .85. Although the STAT was originally developed for children between age two and three years of age, one paper has shown its utility for children between one and two years, and the authors continue to refine its structure and scoring for future reports (Stone, pers. comm.). The original papers restricted prediction to Autistic Disorder, but the study about

younger children extended the prediction to ASD with good ROC statistics. Using a cutoff of 2.75, Se = .95, Sp = .73, PPV = .56, NPV = .97. Excluding the 12 – 13 month-olds: Se = .93, Sp = .83, PPV = .68, NPV = .97. The STAT requires an investment of time and money to train front-line providers; however, once this is accomplished, presumably the administrator has a skill set that facilitates identification and referral for ASD and DD independent of the actual screener application. The STAT has sufficient beginning support to recommend it as a promising tool for use in clinical settings.

Parent Observation of Early Milestone (POEMS)

The POEMS is a medium-length parent checklist (61 items) for very early ASD detection. Although Se and Sp did not reach ideal levels (>.80) at any age, it was the closest at 18 months**,** with Se at .89 and Sp .65; Se is considered more important if it is assumed that it is preferable to not miss cases even if others are over-identified. It is noteworthy that the Se and Sp were around .70 at 12 months of age, given the difficulty of detecting ASD specifically at this early an age through a parent checklist. For the sake of developing the measurement tool, the authors gave the checklist every three months, but presumably a choice would be made as to the ideal time to use the instrument for screening. However, the repeated parent reporting used in the instrument's development also may have served to heighten parents' observational skills, thus increasing accuracy of their reporting, and this would not be the case for a one-time administration. The POEMS is a recently developed measure that may be of use for high-risk infants and future studies may refine its utility.

Autism Detection in Early Childhood (ADEC)

The ADEC is a clinician-interaction instrument. It would appear to require some up-front time for the administrator to familiarize him- or herself with the instrument and to practice using it for a while. Once one is trained or self-trained using the manual, the procedure reportedly takes 10-15 minutes. There are two papers with the English version. In the first one the Se was 1.0 and Sp was .74 – 90 across different groups. However, the ROC coefficients were only determined for more clear cases of ASD (what was Autistic Disorder in DSM-IV terminology and criteria), thus it is difficult to compare it to other instruments that endeavor to include milder cases as well. The second paper/study did include milder children as evidenced through reported developmental scores as well as using an ASD group. With this group Se was .94 but Sp lower at .63. Using a higher cut-off (14), associated with the ADEC category of "high risk of ASD": Se = .85, Sp = .79. Overall the research designs for the studies were relatively strong. Therefore, the ADEC is a promising tool that can be recommended for use, but more research is needed to support and further current evidence.

Assessment for Autism Spectrum Disorders in Young Children

Published Research Evaluating Early Screening Instruments for Autism: Years 1999-2014

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B. Assessment for Autism Spectrum Disorders in Young Children: Methods and Results of Updated Literature Review and Appraisal for Assessment Instruments.

B.1 Literature search

Two phases of literature search were done. The first PI conducted a systematic literature search though the University of Albany using PsycINFO, ERIC, MEDLINE, and PubMed, and with search terms that returned abstracts on the following instruments:

1. Autism Diagnostic Observation Schedule (ADOS), Lord et al., 2000
2. Autism Diagnostic Interview, Revised (ADI-R), Rutter et al., 2003
3. Autism Spectrum Disorder-Diagnostic for Children (ASDDC), Matson et al., 2008
4. Autism Spectrum Rating Scales (ASRS), Goldstein and Naglieri, 2009
5. Childhood Autism Rating Scale (CARS), Schopler et al., 1980
6. Checklist for Autism Spectrum Disorder (CASD), Mayes, 2012
7. Diagnostic Interview for Social and Communication Disorders, Leekham, 2002
8. Gilliam Autism Rating Scale (GARS), Gilliam, 1995
9. Psycho-Educational Profile-Revised (PEP-R), Schopler et al., 1990

From the abstract reviews, articles were chosen for in-depth review and abstracted. They were chosen based on the inclusion criteria in Table B-1 below.

Table B-1
CRITERIA FOR SELECTING STUDIES FOR IN-DEPTH REVIEW

- Published in English in a peer-reviewed scientific/academic publication
- Provide original data about efficacy of an assessment method for autism spectrum disorder
- Evaluate an assessment method currently available to providers in the U.S.
- Provide an adequate description of the assessment methods evaluated, or provide a reference where such a description could be found
- Evaluate subjects of appropriate age, that is, primarily children under three years of age
- Compare the findings of the test to an adequate reference standard**
- Conduct a Receiver Operator Characteristics (ROC) analysis, that is, report the sensitivity and specificity or positive predictive value of the test compared to an adequate reference standard OR provide enough data so that these can be evaluated
- Provide evidence for the instrument's efficacy based on an ROC analysis

** The clinical judgment of an experienced, qualified professional using DSM-IV-TR or DSM-5 was considered adequate, although the majority of articles also use the ADOS and other standardized instruments.

For the second phase, another PI searched more generally for newer and less well-known instruments, using the New York Medical College library. The databases searched included Medline, PubMed, PsycInfo, and ERIC. Once instruments were identified, articles to be included for review were chosen on the basis of the same inclusion criteria as shown in Table B-1.

Selecting articles based on age range, modified to under four years of age.

In the original 1999 ASD Guideline, studies were included that had participants up to six years of age. Since then, a sufficient number of studies have been conducted such that focusing on the more relevant birth-to-

three population is possible. Therefore, the age range criterion was modified to studies that had a preponderance of children three years old and under. To select articles, then, the proportion of children under four years old, three years old, and two years old, was calculated for each individual study (in the case of when only age means and standard deviations were available, proportions were estimated). A criterion of a minimum of 20% of children under four years of age was set for a study to be included.

The original instruments identified and associated articles, as well as newly identified instruments and articles, are shown in Table B-2, minus articles eliminated based on the new age criterion.

Table B-2: Assessment Instruments and Articles
ADOS-2: Autism Diagnostic Observation Schedule, 2nd Edition
Gotham, K., Risi, S., Dawson, G., Tager- Flusberg, H., et al. (2008)
Gotham, K., Risi, S., Pickles, A., & Lord, C. (2007)
Overton, T., Fielding, C., & Garcia de Alba, R. (2008)
Luyster, R., Gotham, K., Guthrie, W., Coffing, M., Petrak, R., Pierce, K., Bishop, S., Esler, A., Hus, V., Oti, R., Richler, J. & Risi S. (2009)
deBildt, A., Sytema, S., van Lang, N. D. J., Minderaa, R. B., van Egeland, H., & de Jonge, M.V. (2009)
ADI-R: Autism Diagnostic Interview-Revised
Lord, C., Pickles, A., McLennan, J., Rutter, M., Bregman, J., Folstein, S., et al. (1997)
Kim, S. H., Thurm, A., Shumway, S., & Lord, C. (2013)
Kim, S, H. & Lord, C. (2012)
ADOS and ADI-R Combined
Kim, S. H. & Lord, C. (2012)
Gray, K. M., Tonge, B. J., Sweeney, D. J. (2008)
CARS, CARS-2: Childhood Autism Rating Scale
Chelbowski, C., Green, J. A., Barton, M. L., & Fein, D. (2010)
Perry, A., Condillac, R. A., Freeman, N. L., Dunn-Geier, J., & Belair, J. (2005)
Ventola, P. E., Kleinman, J., Pandey, J., Barton, M., Allen, M., Green, J., Robbins, D., & Fein, D. (2006)
PDDBI: P DD Behavior Inventory
Cohen, I. L., Gomez, T. R., Gonzalez, M. G., Lennon, E. M., Karmel, B. Z., & Gardner, J. M. (2010)
Cohen, I.L., Schmidt-Lackner, S., Romanczyk, R., & Sudhalter, V. (2003)
Reel, K. H., Lecavalier, L., Butter, E., & Mulick, J. A. (2012)
AMSE: Autism Mental Status Exam
Grodberg, D., Siper, P., Jamison, J., Buxbaum, J. D., & Kolevzon, A. (2015)

Table B-3 shows autism-specific instruments not reviewed and the reasons for not including them.

Table B-3: Assessment Instruments Not Reviewed		
Name, Author	Ages Targeted and Administration Type	Reasons for Exclusion
Autism Spectrum Rating Scales (ASRS, Goldstein & Nalglieri, 2010).	Parent checklist, ages 2-5 and 6 – 18 years	• No published ROC studies
Diagnostic Interview for Social and Communicative Disorders (DISCO, Wing, Leekam, Libby, Gould, & Larcombe. 2002; Wing, 2006).	Clinician Interview 3+ years	• Not easily available in the US, primarily used in the UK • For children three years and older
Gilliam Autism Rating Scale (GARS 1-3, Gilliam, J. E., 2004))	Parent Checklist 3+ years	• Children over 3 years old • No published ROC studies
Social Communication Questionnaire (SCQ, Rutter, Bailey, & Lord, 2003)	Parent Checklist 4+	• Studies suggest lack of utility for children 3 years and younger.

Table B-3: Assessment Instruments Not Reviewed		
Temperament and Atypical Behavior Scales (TABS, Bagnato, Neisworth, Salvia, & Hunt, 1999)	Parent Checklist 11 - 71 months	• No published ROC studies
ROC= Receiver operator characteristics		

B.2 Considerations for the Review of Evidence

This update reviewed assessment instruments only if there were published peer-reviewed articles that reported ROC, sensitivity and specificity, and/or PPV/NPV.

B.3 Assessment Instrument Reviews

For this review, each assessment instrument was described and then critiqued in the following way. The extant literature on the instrument was examined including studies on the instrument's development, how it is administered and scored, and how the constructs it measures are described. Then the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (Whiting, Rutjes, Westwood, et al., 2011) was adapted in the following way: (1) the four domains of Participants, Index Test (the assessment tool), the Reference Standard (the "gold standard") and Timing and Flow were used as units of review with the additional domains of Evaluation and Performance; (2) probe questions were developed for each of the domains; and, (3) the probe questions were applied to each study and conclusions were summarized.

Table B-4 shows the probe questions developed for this review and their significance.

Table B-4a: Probe Questions	
PROBE QUESTIONS	**SIGNIFICANCE**
Was the sample appropriate in size and scope?	
How representative were the children and families in terms of demographics?	Enables generalizability.
Did researchers use a sample matched for developmental level?	When discriminating ASD from DD, some test items may be associated with lower developmental level rather than specific to ASD since the ASD samples tend to have lower developmental attainments than all other groups.
How representative was the sample in terms of cognitive/developmental level?	Results will differ depending on the cognitive and autism severity level of the sample.
Assessment instrument	
Was there anything about how the test was administered that would differ from its intended use in a non-research, community setting?	Examples: extensive training given to providers, research assistants collecting data, items being part of a larger questionnaire, parents being sensitized to ASD symptoms.
Reference Standard	
Did all children receive a Best Estimate Diagnosis (BED) from in-person evaluations? How extensive was the information available to the clinician making the BED?	(Some studies used diagnoses resulting from community-based clinicians.) How "gold" the gold standard is can vary along a continuum. The gold standard appears to be Best Estimate Clinical Diagnosis, but informed by the ADOS and possibly the ADI-R plus other disciplinary evaluations.

Table B-4a: Probe Questions	
PROBE QUESTIONS	**SIGNIFICANCE**
Were the reference standard evaluators blind to the screener risk status of the children?	Bias could occur if the evaluators were aware of the test results.
What diagnostic outcome categories were used to test prediction from screener to reference standard? How were different severity presentations of ASD addressed?	The most informative comparisons include ASD and other DDs and TD children. Studies varied in how different severity levels of ASD were included for prediction.
Timing and Flow	
Was there excessive attrition between testing and gold standard evaluation?	If so, it would be important to know if some systematic source of attrition could lead to bias.
Were there conditions besides attrition that filtered the negative and positive outcomes from the test to the reference standard diagnostic phase?	This would include other tests and procedures, or, for example, physicians referring for evaluation even if screen was negative.
Calculating ROC coefficients	
Was the calculation of sensitivity and specificity supported by available data?	
Were separate calculations made for the younger children?	The youngest children (12-18 months and below) pose the greatest challenge to measurement and prediction.
What was the predictive performance of this test?	
ROC characteristics-what was reported?	Se, Sp, PPV, NPV
Developmental level of children who were true positives?	This will help to compare diagnostic tests in terms of which children are being detected (more or less delayed).
Percent of false positives with other developmental delays?	Who is being misidentified?
ASD=autism spectrum disorder; DD=developmental delay; BED=Best Estimate Diagnosis; ADOS=autism diagnostic observation schedule; ADI-R=autism diagnostic interview-revised; TD=typically developing; ROC=receiver operator characteristics; Se=sensitivity; Sp=specificity; PPV=positive predictive value; NPV=negative predictive value;	

B.4 Results of Research Reviews of Autism Assessment Instruments

Table B-4 summarizes the methods and findings for the screening instrument studies reviewed. Table B-15 shows the results from applying the research probe questions.

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
Autism Diagnostic Observation Scale-2	15 mos-adulthood	Semi-structured standardized observational, clinician-administered	Gotham, Risi, Pickles, & Lord, 2007 Module 1- 3, Goal: to revise algorithms for better prediction and more independence from age and cognitive level.	For prediction to Autistic Disorder, all Se and Sp in .90's except for one .84. For PDD-NOS, fair —from .72 to .95. However, for	Large sample from multi-site study. Age Range 14 months to 16 years. ASD=912, PDD-NOS etc.=439, DD=279. Reference standard was BED. Groups were AD, non-AD ASD, and non-ASD DD. All methods adequate except for the fact that the reference test (ADOS)

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
				youngest and lowest MA, specificity unacceptable. *"…the specificity of classification in children with non-verbal ages 15 months and younger remained weak. For these children, ADOS cut-offs do not reliably differentiate Autism or ASD from other disorders."* Module 1 still not independent of age effects.	was also used in determining the gold standard diagnosis. The authors presented a rationale for why that was necessary. Caution is needed in using original algorithms, and the revised algorithms appear superior.
			Gotham, Risi, Dawson, et al., 2008 Goal: To validate revised algorithms on a large independent sample.	For prediction to Autistic Disorder, all sensitivities and specificities in .80's and .90's with few exceptions to 70's. For PDD-NOS, Se and Sp lower, ranging from .72 to .84. Still some low prediction for youngest and mildest children.	Large sample, N=1281, in Module 1 & 2, 461 were 18 months-5 years. Reference standard was BED, using ADI-R, ADOS, and cognitive testing. Some small cell sizes for younger and milder children and discrepancies that appeared to be differences in scoring RRBs at one site.
			Gray, Tonge, & Sweeney, 2008 Goal: To evaluate the diagnostic validity of the ADI-R and the ADOS in young children. However, the two instruments were examined separately and not in combination	ADOS Modules 1 and 2 ROC varied, depended on numerous group predicted to (AD vs. non-autism or ASD vs, non-ASD AND no words vs some words AND using SA domain only vs	All participants aged 20-55 months. (Included children >3 yrs). N=209. Differences were examined for autism versus non-autism (including PDD NOS) groups, and separately for autism, PDD NOS, and non-Autism Spectrum Disorder (non-ASD) groups. ADI-R and ADOS diagnostic classifications were compared to consensus clinical diagnoses. Clinicians

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
				SA & RRB). Se high for all group (.88-.98) except for ASD vs non-ASD, Some Words group: .76 & .78. Sp had opposite pattern with .86 - .96 except for AD vs non-AD for No Words group: .73 & .82.	were blind to total scores of ADI-R and ADOS.
			Luyster et al., 2009 Goal: To present reliability and validity data for the Toddler Module.	Across all groups and all comparisons, Se and Sp .87 - .94, most in .90's.	Participants all aged 16 – 30 months. Medium to small sample depending on cell. Reference standard was BED, using ADI-R, ADOS, and cognitive testing.
			de Bildt et al., 2009 Goal: To investigate the sensitivity and specificity of the revised algorithms of the ADOS using an independent sample of Dutch children.	Results indicate an improved balance in sensitivity and specificity in the revised algorithms for modules 2 and 3. <u>Module 1</u>, AD vs non-spectrum, the revised algorithms have slightly higher sensitivity than the original (.82-.92), and lower specificity (.71-.88). <u>Module 2</u>, AD vs. non-spectrum, sensitivity is increased (.63 - .88), and specificity decreased (.76 - .92) compared to the original.	Large independent sample (N=558) Dutch children ranging in age from 13-198 months. 3 groups, Module 1, Some Words, Module 2, 5 and Older and Module 3. Reference standard was BED, using the DSM-IV, ADI-R, ADOS and cognitive testing.
ADI-R					

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
Autism Diagnostic Interview-Revised	All ages starting at develop-mental level of 24 months (scoring different for 2 yr olds - 4 yr olds and 4 yr olds +) Minimum mental age of 24 mos	Parent Interview, standardized, semi-structured	Gray, Tonge & Sweeny, 2008 Goal: To evaluate the diagnostic validity of the ADI-R and the ADOS in young children. However, the two instruments were examined separately and not in combination.	ADI-R prediction between AD vs. non-ASD was low: Se and Sp of ADI predicting to first AD then ASD ranged from .70-.77.	All participants aged 20-55 months. (Included children >3 yrs). N=209. Differences were examined for autism versus non-autism (including PDD NOS) groups, and separately for autism, PDD NOS, and non-Autism Spectrum Disorder (non-ASD) groups. ADI-R and ADOS diagnostic classifications were compared to consensus clinical diagnoses. Clinicians were blind to total scores of ADI-R and ADOS.
			Kim & Lord, 2012 Goal: To improve ADI-R prediction and classification for young children using large multisite samples	Clinical cutoffs: Se .80 - .94 and Sp .70 - .81 for ASD vs. NS depending on developmental cells. Research cutoffs: Se .80 - .84 and Sp .82 - .90.	Participants all aged 12–47 months with a nonverbal mental age of at least 10 months. Large sample size: reference standard was BED using ADI-R, ADOS, and cognitive testing. Reference standard clinicians not blind to ADI-R scores.

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
			Kim, Thurm, Shumway, & Lord, 2013 Goal: To replicate the findings based on new ADI-R algorithms for toddlers and young preschoolers in two different multisite datasets	Study 1: Clinical cutoffs: Se .85 - .96 and Sp .83 - .94 depending on developmental cells & group comparisons. Research cutoffs: Se .72 - .86 and Sp .92 - .94. Study 2: Clinical cutoffs: Se .89 - .100 and Sp .64 - .76 (youngest children with lowest Sp) depending on developmental cells & group comparisons. Research cutoffs: Se .69 - .97 and Sp .64 - .89.	Participants all aged 12-47. Study 1 large, 10-site sample (N=641), BED of ADI-R, ADOS and cognitive testing. Study 2 sample smaller (N=168) with some TD cells too small (N=0, 2, 8). Same BED. Reference standard clinicians not blind to ADI-R scores.
ADI-R and ADOS combined					
ADI-R and ADOS-2 combined	ADOS2: 15 mos-adulthood ADI-R: All ages starting at developmental level of 24 mos (scoring different for 2 yr olds - 4 yr olds vs. 4 yr olds +)	These instruments are meant to complement each other since one is direct clinician administration and the other is a parent interview.	Kim & Lord, 2012 Goal: To systematically examine combined use of the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) for children under age 4 using newly developed and revised diagnostic algorithms.	(a) Meeting ADI-R criteria (b) Meeting ADOS criteria (c) Meeting either ADI-R or ADOS criteria = excellent sensitivities for ASD cases (97%–99%), but poor specificities (45%–85%). (d) Meeting criteria on both the ADI-	All participants aged 12-47 months. Large sample size (N=604). Participants were divided into three developmental cells by the child's age and language level following the structure of the developmental groupings of the new ADI-R algorithms. Reference standard was BEC (Best Estimate Clinical diagnosis), using ADOS, ADI-R and NVIQ.

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
				R and ADOS. = Se and Sp for ASD versus NS were consistently above .80. Across all test groups, the combination of using ADI-R *and* ADOS resulted in significantly improved specificity.	
CARS & CARS-2					
Childhood Autism Rating Scale-2	2-16 yrs old	Clinician judgment after observation	Perry, Condillac, Freeman, Dunn-Geier, & Belair, 2005 Goals: To: 1) assess the degree of concordance between autism diagnosis defined by DSM-IV and the CARS among young children, and 2) assess the extent to which the CARS related to the children's developmental level and 3. assess whether the CARS differentiates among children with different diagnoses.	Using the DSM-IV to be the "true diagnosis" Se = .94 Sp= .85	Examined a large sample (N=274) of preschool children ages 2-6 years. All participants received a BED from in-person evaluations including information from cognitive testing and Vineland in addition to direct observation and interaction. Method weaknesses included the fact that <100% of BED were done by clinicians blind to CARS scores and that there were no separate analyses for younger vs older children, despite only 6% of the participants being between 2 and 3 yr olds. About 1/3 were between the ages of 3 and 4 yr olds and the rest were older.
			Ventola, Kleinman, Pandey, Barton, Allen, Green, Robbins, & Fein, 2006 Goal: To compare diagnostic measures (ADOS-G, ADI-R, CARS, and clinical judgment using DSM-IV applied to toddlers. Both for the diagnosis of Autistic Disorder and for the diagnosis	<u>CARS cut-off of 30 and Autistic Disorder only BED</u> Se = .96 Sp = .67 <u>CARS cut-off of 30 and Autistic Disorder + PDD-NOS BED</u> Se= .89 Sp =1.00	All participants 16 – 30 mos; moderate sample size (n=45). Methods adequate except that main risk for bias was that reference standard examiners were not blind to CARS scores.

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
			of either Autistic Disorder or PDD-NOS, the ADOS –G and CARS had good Se, and the ADI-R had relatively poor Sp. All measures had similar Se rates, but the Sp for the CARS was slightly higher for the diagnosis of Autistic Disorder or PDD-NOS.		
			Chelbowski, Green, Barton, & Fein, 2010 Goals: To 1) replicate studies that have established cut-off scores for toddler and preschool-aged children, and 2) calculate Se, Sp, and positive and negative predictive value for the optimal cut-off scores, and 3) test the obtained cut-off scores for agreement with ADOS scores and with clinical judgment DSM-IV diagnoses.	2-YR OLDS 4 YR OLDS *AD 32* *For AD, 30* Se=.79 Se=.86 Sp=.80 Sp=.80 *ASD, 25.5* *ASD, 25.5* Se=.93 Se=.84 Sp=.85 Sp=.93	Measured two large, high-risk samples using diagnostic outcome categories of Autism, PDD-NOS, DD and No Diagnosis. One group approx. 2 yo (N=376, ranged between 21-30 mos) and other group approx. 4 yo (N=186, ranged between 42-66 mos). All participants received BED from in-person evaluations including information from ADOS and Mullen. Reference standard clinicians not blind to test scores.
PDDBI					
PDD Behavior Inventory	2-12 years	Parent/Caregiver completed rating scale	Cohen, Gomez, Lennon, Karmel, & Gardner, 2010 Goal: To assess the diagnostic validity of the parent version of the PDDBI and to understand the benefits and limitations of this assessment tool.	Se and Sp was strongest comparing Autism vs. NS compared to Autism vs. PDD-NOS. The majority of the coefficients were above .80 and .90. Age-matched group showed optimal cutoff was 42.	Sample size good (N= 73, ranging from 18-60 mos however only 6% <2yo); not known if gold standard evaluators were blind to PDDBI score status; reference standard BED/DSM with ADOS and ADI-R; They reported cognitive level differences among groups, and did make a cognitively matched group for one set of ROC analyses.

Table B-4b: Research Summary for Assessment Instruments					
Instrument	**Ages**	**Administration**	**Article**	**Se, Sp, PPV**	**Research Summary**
ADOS-2 Module 1 & 2 and Toddler Module					
			Reel, Lecavalier, Butter, & Mulick, 2012 Goal: To assess the diagnostic utility of the PDDBI with particular interest in the instrument's ability to differentiate ASD from non-ASD.	Optimal sensitivity and specificity were achieved using a cutoff score of 45 on the Autism Composite T-score. Diagnostic accuracy was not good (sensitivity = .74, specificity = .62, efficiency = .68), but better in individuals with NV IQ < 70.	Examined the PDDBI using ROC with a moderate sample size (n=84). Age range of the children made the article of low applicability to our review (only 31% < 4 yo).
AMSE					
			Grodberg, Siper, Jamison, Buxbaum, & Kolevzon, 2015	Goal: To establish the diagnostic accuracy of the AMSE in a population of young children. Optimal cutoff score was established at 6, producing a Se of .94 and a Sp of 1.00.	Small sample size (n=45) ranging in age from 18-60 months. All participants received a BED from in-person evaluations with extensive information included. Used diagnostic outcome categories of ASD and non-ASD. All reference standard evaluators were blind to the screener risk status of the participants.

Se=sensitivity; Sp=specificity; PPV=positive predictive value; ADOS= autism diagnostic observation scale; ASD=autism spectrum disorder; MA=mental age; PDD-NOS=pervasive developmental disorder-not otherwise specified; DD=developmental delays; BED= best estimate diagnosis; N=large sample size; n= moderate sample size ; ADI-R= autism diagnostic interview-revised; BED=best estimate clinical diagnosis; NVIQ=nonverbal IQ ; CARS= Childhood Autism Rating Scale; AMSE=Autism Mental Status Exam ; PDDBI=pervasive developmental disorder behavior inventory;

Table B-5a: Probe Questions for the **ADOS**					
PROBE QUESTIONS	Gotham, Risi, Pickles, & Lord, 2007.	Gotham, Risi, Dawson, et al., 2008.	Gray, Tonge, & Sweeney, 2008.	Luyster et al., 2009.	de Bildt et al., 2009
PARTICIPANTS					
Was the sample appropriate in size and scope?	Large sample (N=1,139) from multi-site study. Age range 14 months to 16 years.	Large sample (N=1281). In Module 1 & 2., 461 were 18 mos-5 yrs.	209 children aged 20– 55 months. Autistic Disorder: N= 120	N=182 participants between 12 and 30 months split into three groups: TD,	Large independent sample (N=558) of Dutch children ranging from 13-198 months split

Table B-5a: Probe Questions for the **ADOS**					
PROBE QUESTIONS	Gotham, Risi, Pickles, & Lord, 2007.	Gotham, Risi, Dawson, et al., 2008.	Gray, Tonge, & Sweeney, 2008.	Luyster et al., 2009.	de Bildt et al., 2009
	ASD=912, PDD-NOS etc.=439, DD=279. Because older adolescents and adults with ASD were seen as a behaviorally distinct group that merited individual study, Module 4 recipients were excluded. The final dataset included 912 cases.		Non-Autism: N=89, with 23 having a diagnosis of PDD NOS, with the remainder with developmental delay and/ or language impairment.	non-spectrum disorders, and ASD.	into 3 groups: Module 1 some words, Module 2, 5 and Older, and Module 3.
Did investigators use a sample matched for developmental level?	Yes	Yes	Developmental age of groups was significantly different so they used developmental age as a covariate in their analyses.	Verbal and nonverbal children split into different groups based on language equivalents.	Yes, following the homogeneous cell division conducted by Gotham et. al.
ASSESSMENT INSTRUMENT					
Was there anything about how the instrument was administered that would be different from its intended use in a non-research, community setting?	No	No	No	No	No
Were there any issues regarding the way it is scored in the study?	No	Some small cell sizes for younger and milder children and discrepancies that appeared to be differences in scoring RRB's at one site.	No	No	No
REFERENCE STANDARD					
Did all children receive a BED from in-person evaluations? How extensive was the information available to the clinician making the	Yes. BED used the ADI-R, Mullen Scales of Early Learning, and Vineland.	Yes. BED, used the ADI-R, ADOS, and cognitive testing.	Yes. BED used PEP-R, RDLS, and DBC-P. Diagnoses were made according to the DSM-IV criteria for Autistic	Yes. BED used the ADI-R and Mullen Scales of Early Learning.	Yes. BED used the ADI-R, ADOS, and cognitive testing.

Table B-5a: Probe Questions for the **ADOS**					
PROBE QUESTIONS	Gotham, Risi, Pickles, & Lord, 2007.	Gotham, Risi, Dawson, et al., 2008.	Gray, Tonge, & Sweeney, 2008.	Luyster et al., 2009.	de Bildt et al., 2009
Best Estimate Diagnosis?			Disorder. One of two clinicians gave the ADI-R, with the second clinician giving the ADOS.		
Were the reference standard evaluators blind to the assessment results of the children?	Clinicians were not blind to the assessment results of the children. Clinicians involved in each case together determined a BED after review of all information.	Clinicians were not blind to the assessment results of the children.	Clinicians were blind to the total scores of the ADI-R and ADOS assessments during the case conferencing process.	Clinicians were blind to child's history and diagnostic status. A percentage of administrators were videotaped and coded by blind raters who established interrater reliability.	Not reported
What diagnostic outcome categories were used to test prediction from assessment instrument to reference standard?	Groups were AD, non-AD ASD, and non-ASD DD. Non-spectrum diagnoses included mental retardation, language disorders, and fragile X syndrome, among others.	Autism, Non-Autism, Non-ASD DD	Autism, Non-Autism (includes PDD-NOS for some analyses and separating PDD-NOS and AD for others)	TD, Non-ASD, ASD	Autism, ASD, Non-ASD
TIMING AND FLOW					
Was there excessive attrition through any phase of assessment and evaluation?	No	No	No	No	No
Were there conditions besides attrition that filtered the negative and positive scores from the testing to the reference standard diagnostic testing phase?	No	No	No	No	No
EVALUATION					

Table B-5a: Probe Questions for the **ADOS**					
PROBE QUESTIONS	Gotham, Risi, Pickles, & Lord, 2007.	Gotham, Risi, Dawson, et al., 2008.	Gray, Tonge, & Sweeney, 2008.	Luyster et al., 2009.	de Bildt et al., 2009
How were performance/ predictive values calculated?	Roc curves for Se and Sp were calculated.	Predictive validity was assessed with ROC curves to obtain Se and Sp of both the old and the new algorithms by cell.	Efficacy of the ADI-R and ADOS algorithms compared to consensus clinical diagnosis autism versus non-autism, and to ASD (autism and PDD NOS) versus non-ASD, was evaluated in terms of Se, Sp, overall efficiency, predictive value of a positive test (PVP), and predictive value of a negative test (PVN).	ROC curve analysis established a cutoff score of 12 for nonverbal toddlers and cutoff of 10 for verbal toddlers to calculate Se and Sp.	Predictive validity was assessed with Se and Sp of the revised algorithms.
Was performance/prediction for younger versus older children explored?	Yes	No	No	No	No
PERFORMANCE					
What were the performance/predictive values?	For prediction to Autistic Disorder, all Se and Sp in .90's except for one .84. For PDD-NOS, lower—from .72 to .95. However, for youngest and lowest MA, Sp unacceptable. *"…the specificity of classification in children with non-verbal ages 15 months and younger remained weak. For these children, ADOS cut-offs do not reliably differentiate Autism or ASD from other*	For prediction to Autistic Disorder, all Se's and Sp's in .80's and .90's with few exceptions to .70's. For PDD-NOS, Se and Sp lower, ranging from .72 to .84. Prediction was lowest for youngest and mildest children.	Reducing the Repetitive domain threshold cut-off score from three to two, resulted in a Se of .82, Sp of .58. Overall correct classification rate of .72), PPV of .73, and NPV of .70.	A cutoff score of 12 for nonverbal toddlers resulted in a Se of .91 and Sp of .91. Verbal toddlers' cutoff of 10 appeared to yield a best Se and Sp (.88 and .91, respectively).	Results indicate an improved balance in Se and Sp in the revised algorithms for modules 2 and 3. Module 1, AD vs. non-spectrum, the revised algorithms have slightly higher Se than the original (.82-.92), and lower Sp (.71-.88). Module 2, AD vs non-spectrum Se increased (.63-.88), and Sp decreased (.76-.92) compared to the original.

Table B-5a: Probe Questions for the **ADOS**					
PROBE QUESTIONS	Gotham, Risi, Pickles, & Lord, 2007.	Gotham, Risi, Dawson, et al., 2008.	Gray, Tonge, & Sweeney, 2008.	Luyster et al., 2009.	de Bildt et al., 2009
	disorders." Module 1 still not independent of age effects.				
What was the developmental level of children detected?	Not reported	Not reported	<u>Autism (n=120)</u> Developmental age range:4-48 Developmental age (SD): 20.57 (8.35) <u>Non-Autism (n=89)</u> Developmental age range (months): 14-46 mos Developmental age (SD): 28.97 mos (8.86)	Not reported	Not reported
Of the false positives for ASD, what proportion had other developmental or learning disabilities?	Not reported	Not reported	Twelve (44%) of the ADI-R false positive cases received a clinical diagnosis of PDD-NOS. The false positive group had a significantly higher developmental age (M = 29.31, SD = 9.02) than the remainder of the sample (M = 23.32, SD = 9.35) and had significantly higher levels of behavior and emotional problems) as measured by the total score of the DBC. 63% percent of the false positives were developmentally delayed, and all except for two (93%) had delayed language.	Not reported	Not reported

Table B-5b: Probe Questions for the ADI-R	
PROBE QUESTIONS	Kim, Thurm, Shumway, & Lord, 2013
PARTICIPANTS	
Was the sample appropriate in size and scope?	Study 1: Data from a network of 10 sites, N=641, ages 12 – 47 mos. ASD : N=526 Non-ASD, DD : N=70 TD: N=45 Study 2: Data from an NIMH study, ages 12 – 47 mos. ASD: N=168 Non-ASD DD: N=52 TD: N=8
Did investigators use a sample matched for developmental level?	Yes. They stratified by age and verbal level to mitigate effects of age and IQ on autism scores.
How representative was the sample?	Study 1: 77% male, 80% white Study 2: sex not reported, 73% white
ASSESSMENT INSTRUMENT	
Was there anything about how the screener was administered that would be different from its intended use in a non-research, community setting?	No
Were there any issues regarding the way it is scored in the study?	No
REFERENCE STANDARD	
Did all children receive a BED from in-person evaluations? How extensive was the information available to the clinician making the Best Estimate Diagnosis?	Yes. BED using ADOS, ADI-R, and NVIQ.
Were the reference standard evaluators blind to the screener risk status of the children?	No
What diagnostic outcome categories were used to test prediction from assessment instrument to reference standard?	ASD, NS (DD and ID), TD
TIMING AND FLOW	
Was there excessive attrition through any phase of evaluation?	No
Were there conditions besides attrition that filtered the negative and positive scores from the original testing to the reference standard diagnostic testing phase?	No
EVALUATION	
How were performance/ predictive values calculated?	Calculation of Se and Sp supported by available data.
Was performance/prediction for younger versus older children explored?	Yes
PERFORMANCE	
What were the performance/predictive values?	Study 1: Clinical cutoffs: Se .85 - .96 and Sp .83 - .94 depending on developmental cells and group comparisons. Research cutoffs: Se .72 - .86 and Sp .92 - .94. Study 2: Clinical cutoffs: Se .89 - .100 and Sp .64 - .76 (youngest children with lowest Sp) depending on developmental cells and group comparisons. Research

Table B-5b: Probe Questions for the ADI-R	
PROBE QUESTIONS	Kim, Thurm, Shumway, & Lord, 2013
	cutoffs: Se .69 - .97 and Sp .64 - .89
What was the developmental level of participants?	N/A
Of the false positives for ASD, what proportion had other developmental or learning disabilities?	N/A

Table B-5c: Probe Questions for the ADI-R and ADOS in Combination		
PROBE QUESTIONS	Gray, Tonge, & Sweeney, 2008	Kim & Lord, 2012
PARTICIPANTS		
Was the sample appropriate in size and scope?	N=209, ages 20–55 mos. Autistic Disorder: N= 120 Non-Autism: N=89, with 23 having a diagnosis of PDD-NOS, with the remainder with developmental delay and/ or language impairment.	N=695, ages12–47 mos with a nonverbal mental age of at least 10 months. ASD: N=491 Non-ASD DD: N=136 TD: N=67
Did investigators use a sample matched for developmental level?	Yes. Developmental age of groups was significantly different so they used developmental age as a covariate in their analyses.	Yes. They created three developmental cells to obtain more homogeneous groups to reduce the effect of language level and age. These groups were defined by age and verbal status during the assessment: “no speech,” ‘‘single words,” and ‘‘phrase speech.”
How representative was the sample?	Autism (n=120) 85% male Non-Autism (n=89) 81 % male Ethnicity not reported	77% male 78% Caucasian
ASSESSMENT INSTRUMENT		
Was there anything about how the screener was administered that would be different from its intended use in a non-research, community setting?	No	No
Were there any issues regarding the way it is scored in the study?	No	No
REFERENCE STANDARD		
Did all children receive a BED from in-person evaluations? How extensive was the information available to the clinician making the Best Estimate Diagnosis?	Yes. BED used PEP-R, RDLS, and DBC-P.	Yes. BED using ADOS, and ADI-R.
Were the reference standard evaluators blind to the screener risk status of the children?	Clinicians were blind to the total scores of the ADI-R and ADOS assessments during the case conferencing process.	No
What diagnostic outcome categories were used to test prediction from assessment instrument to reference standard?	Autism, Non-Autism (includes PDD-NOS for some analyses and separating PDD-NOS and AD for others)	ASD, Non-ASD DD, and TD
TIMING AND FLOW		

Table B-5c: Probe Questions for the ADI-R and ADOS in Combination		
PROBE QUESTIONS	Gray, Tonge, & Sweeney, 2008	Kim & Lord, 2012
Was there excessive attrition through any phase of evaluation?	No	No
Were there conditions besides attrition that filtered the negative and positive scores from the original testing to the reference standard diagnostic testing phase?	No	No
How were performance/ predictive values calculated?	Efficacy of the ADI-R and ADOS algorithms compared to consensus clinical diagnosis autism versus non-autism, and to ASD (autism and PDD NOS) versus non-ASD, was evaluated in terms of Se, Sp, PPV, and NPP.	ROC curves were calculated to examine the Se and Sp of the selected cutoff scores.
Was performance/prediction for younger versus older children explored?	No	Yes
PERFORMANCE		
What were the performance/predictive values?	Reducing the Repetitive domain threshold cut-off score from three to two, resulted in a Se of .82, Sp of .58 (95% CI .47–.69), overall correct classification rate of .72 PPV of .73, and NPV of .70.	The clinical cutoffs yielded Se's ranging from .80 to .94 and Sp's ranging from .70 to .81 for ASD depending on developmental cells. For research cutoffs, Se's ranged from .80 to .84 and Sp's ranged from .82 to .90.
What was the developmental level of participants?	<u>Autism (n=120)</u> Developmental age range: 4-48 mos. Developmental age (SD): 20.57 mos. (8.35) <u>Non-Autism (n=89)</u> Developmental age range: 14-46mos Developmental age (SD): 28.97 mos. (8.86)	N/A
Of the false positives for ASD, what proportion had other developmental or learning disabilities?	Twelve (44%) of the ADI-R false positive cases received a clinical diagnosis of PDD-NOS. The false positive group had a significantly higher developmental age (M = 29.31, SD = 9.02) than the remainder of the sample (M = 23.32, SD = 9.35), t (205) = 3.12, p < .01, and had significantly higher levels of behavior and emotional problems (M = 70.52, SD = 27.44 as opposed to M = 45.29, SD = 25.04) as measured by the total score of the DBC, t (200) = 4.81, p < .001. 63% percent of the false positives were developmentally delayed, and all except for two (93%) had delayed language.	The biggest challenges in discriminating children with ASD were the youngest children, nonverbal children with the most significant delays, and preschool children with more advanced verbal abilities.

Table B-5d: Probe Questions for the Childhood Autism Rating Scale (CARS)			
PROBE QUESTIONS	Perry, Condillac, Freeman, Dunn-Geier, & Belair, 2005	Ventola, Kleinman, Pandey, Barton, Allen, Green, Robbins, & Fein, 2006	Chelbowski, Green, Barton, & Fein, 2010
PARTICIPANTS			
Was the sample appropriate in size and scope?	N=127, ages 2-6 yrs, All high risk, having failed the M-CHAT and Follow-up Interview	N=45, ages 16 – 30 mos	Two large, high risk samples. A) N=376, ages 21-30 mos, B) N=186, 42-66 mos.
Did investigators use a sample matched for developmental level?	No, but they explored the relationship between CARS scores and cognitive and adaptive scores.	Yes	No, but they reported developmental level for each outcome group.
ASSESSMENT INSTRUMENT			
Was there anything about how the instrument was administered that would be different from its intended use in a non-research, community setting?	Yes: They have a semi-standardized interaction approach to test imitation and nonverbal communication. Also, training and reliability checks occurred.	Yes: They used it with children under 24 months (intended for children 24 months+). Reliability checks were done.	No
Were there any issues regarding the way it is scored in the study?	No	No	No
REFERENCE STANDARD			
Did all children receive a BED from in-person evaluations? How extensive was the information available to the clinician making the Best Estimate Diagnosis?	Yes. BED using cognitive testing and Vineland, but no ADOS or ADI-R.	Yes. BED using cognitive testing and Vineland, but no ADOS or ADI-R.	Yes: from in-person evaluations including information from ADOS and Mullen.
Were the reference standard evaluators blind to the assessment results of the children?	Yes/No. Less than 100% of BED were done by clinicians blind to CARS scores.	No. Reference standard examiners were not blind to CARS scores. Also, the evaluators knew that all children had failed the MCHAT.	No. Reference standard clinicians not blind to test scores.
What diagnostic outcome categories were used to test prediction from assessment instrument to reference standard?	Autistic Disorder (AD), PDD-NOS, MR, Delayed, and Other (included ADHD, behavior problems, no dx).	Autistic Disorder (AD), PDD-NOS and non-autistic	Autism, PDD-NOS, DD and No Diagnosis
TIMING AND FLOW			
Was there excessive attrition through any phase of assessment and evaluation?	No	No	No
Were there conditions besides attrition that filtered the negative	No	No	No

Table B-5d: Probe Questions for the Childhood Autism Rating Scale (CARS)			
PROBE QUESTIONS	Perry, Condillac, Freeman, Dunn-Geier, & Belair, 2005	Ventola, Kleinman, Pandey, Barton, Allen, Green, Robbins, & Fein, 2006	Chelbowski, Green, Barton, & Fein, 2010
and positive screens from the original screening to the reference standard diagnostic testing phase?			
EVALUATION			
How were performance/ predictive values calculated?	Se and Sp calculated using DSM-IV as "true diagnosis"	Se and Sp for the CARS was calculated two ways: (1) combining the PDD-NOS group with non-autistic group and only considering the AD group for the criterion, (2) using both AD and PDD-NOS group for ASD group.	Se and Sp were calculated for each group utilizing different cut-off scores.
Was performance/prediction for younger versus older children explored?	No separate analyses for younger vs. older children, despite only 6% of the participants being between 2 and 3 yo. About 1/3 were between the ages of 3 and 4 yo and the rest were older.	Not necessary—all <30 mos	Yes, separated 2 yr old vs. 4 yr old samples. Se and Sp generally higher for four-year-olds AND for < 30 months (16-30 months). The Se was a little lower but Sp remained the same.
PERFORMANCE			
What were the performance/predictive values?	Using the DSM-IV to be the "true diagnosis" the CARS had a Se of .94 and a Sp of .85	CARS cut-off of 30 and BED Autistic Disorder only: Se .96, Sp .66, PPV 81 CARS cut-off of 30 and BED: Autistic Disorder + PDD-NOS Se .88, Sp 1.0	2-YEAR OLDS: <u>For Aut Dis 32</u> Se=.79 Sp=.81 <u>For ASD, 25.5</u> Se=.93 Sp = .85 4-YEAR OLDS: <u>For AD, 30</u> Se=.86 Sp=.80 <u>For ASD, 25.5</u> Se = .84 Sp = .93
What was the developmental level of children detected?	Not reported	**Mullen T Score** / **ASD** / **Non ASD** Exp. Lang 25.1 26.6 Rec. Lang 21.4 29.6 Fin Mot 28.1 40.2 Visual Recep 27.8 42.2 **Vineland Stand Score**	Each group except the non-diagnosed were low; although there were significant

Table B-5d: Probe Questions for the Childhood Autism Rating Scale (CARS)					
PROBE QUESTIONS	Perry, Condillac, Freeman, Dunn-Geier, & Belair, 2005	Ventola, Kleinman, Pandey, Barton, Allen, Green, Robbins, & Fein, 2006		Chelbowski, Green, Barton, & Fein, 2010	
		Comm DLS Soc Mot	64.3 68.1 67.2 81.8	68.6 68.6 75.4 87.4	differences between them, the authors said they were not clinically significant.
Of the false positives for ASD, what proportion had other developmental or learning disabilities?	Not Reported	Not Reported	Not Reported		

Conclusions regarding the research evidence are as follows:

Autism Diagnostic Observation Scale-2

It was decided that the review would proceed from the revised version of the ADOS, since this is what currently in use. Gotham, Risi, Pickles, and Lord (2007) and Gotham, Risi, Dawson, et al. (2008) reported on revised ADOS-2 algorithms for better prediction and less association with cognitive level and age. These goals were accomplished for preschoolers and grade school children, but prediction for the youngest children remained unacceptable. deBildt et al. (2009) validated the ADOS-2 on a large sample of Dutch children for Modules 1, 2, and 3. The article by Luyster et al. (2009) then established the Toddler Module for use. For this paper, research quality was good for all procedures with two weaknesses: medium to small cell sizes and, for all of these studies, the index test was used as part of the diagnostic procedure for the reference test ("incorporation bias"). The authors gave a rationale for the necessity of this procedure. The Toddler Module and Module 1 are recommended for use with young children being evaluated for ASD.

Autism Diagnostic Interview-Revised

Since the ADI-R was first developed (Lord, 1994), it had been shown to be of limited use for younger children. Initially it was indicated that children should have a non-verbal mental age above 24 months, which would be inapplicable for many children with ASD even at 3 years of age. Discrimination between nonverbal children with ASD and nonverbal children without ASD under 2 years of age, especially for those with mental ages under 18 months was poor, resulting in low specificity (Gray, Tonge, & Sweeney, 2008). Kim & Lord (2012) and Kim, Thurm, Shumway, & Lord (2013) added items in order to improve applicability to younger children. Another important goal was to make the autism scores as independent from age and verbal/cognitive ability as possible. The studies used factor analysis, logistic regression, and ROC analysis applied to new algorithms based on the changes. The first study established the new subscales and algorithms for both clinical and research cut-offs, and the second set of studies were replication studies. Greater independence from subject characteristics was achieved, although not to a perfect extent, and Se and Sp was significantly improved; the

improvements were maintained for the most part for the two validation samples. Regardless, prediction remains lowest for the youngest and developmentally lowest groups. As in the ADOS-2 studies, there is a methodological circular situation wherein the index test (ADI-R) is used as part of the reference test (gold standard BED). As a result, the BED clinicians are not blind to the ADI-R scores. In sum, these two papers comprise three moderate-good quality studies with good applicability that support the use of the ADI-R with young children.

Childhood Autism Rating Scale-2

Perry, Condillac, Freeman, Dunn-Geier, & Belair, 2005 conducted a study predicting BED from CARS scores using children ages 2-6. Although the Se and Sp were adequate, only 60% of the children were three years old and under, and no separate analyses were done for the younger children. Both Ventola, et al. (2006) and Chelbowski, Green, Barton, & Fein (2010) examined CARS prediction to ADOS scores and BED and found adequate Se and Sp. Another important contribution was to suggest a lower cut-off score than presented in manual and showed that the youngest children did not have as good prediction to the reference standard as older sample children. The studies all show that the CARS is related to cognitive level and is better at detecting more severe children. It is recommended for use with these cautions in mind.

PDD Behavior Inventory (PDDBI)

The PDDBI is an instrument that has been traditionally used in research and treatment studies. It is parent-rated and consists of 188 items and several subscales that characterize both adaptive and maladaptive behaviors, in addition to autism symptoms. Although the scale starts at age 2, most of the validity studies have predominantly used children preschool aged and older. One article by Cohen et al (2010) demonstrated good predictive validity using ROC analyses; one recent article has not replicated these findings. Therefore, for this instrument to have an evidence base as a diagnostic instrument for toddlers, there would need to be more research in children this age.

Autism Mental Status Exam

This is a new very brief assessment instrument that is to be administered through interaction with a child by an experienced clinician. It consists of the follow eight items: (1) eye contact, (2) interest in others, (3) pointing skills, (4) language, (5) pragmatics, (6) repetitive behaviors, (7) preoccupations, and (8) unusual sensitivities. Each item is scored on a 0-2 scale. The one study focusing exclusively on children under three years of age had a small sample size (ASD=33, Non-ASD=12) but a strong BED and evaluators were blind to the AMSE score. With a cut-off of 6, Se was .94 and Sp was 1.0. It is unusual to get such high ROC with so few items. Due to the small sample size in existing studies, more validating research will be necessary before the AMSE can be recommended.

Report of Research for Interventions for Children with Autism Spectrum Disorders

Review of Empirical Literature of Behavioral Interventions for Children with Autism Spectrum Disorders: Years 2000-2011

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C. Behavior Interventions for Children with Autism Spectrum Disorders

Behavioral interventions draw upon core scientific principles of how people learn and adapt. These principles are derived from research on basic principles of learning, retention, and generalization of learned skills. Behavioral interventions draw upon extensive research on learning principles that emphasize the antecedents and consequences of behavior, the detailed nature of behavior, and its adaptability to the social and physical environment. The social and physical environment in turn provides simple and complex stimuli and simple and complex reactions to behavior. Additionally, behavioral interventions focus on the function of behavior to understand how it is acquired, maintained, and sometimes lost. Further, the teaching of new skills typically involves an analysis of the many component parts of complex behaviors involving communication, emotional development, social development, independence, and knowledge.

Behavioral interventions include those developed in the related areas of behavior therapy, cognitive behavior therapy, and applied behavior analysis. The emphasis in these areas rests upon an evidence-based approach and focus on:

- An understanding of the individual's skill assets and deficits, as well as his/her physical/developmental/medical status
- Teaching skills that promote independence
- An emphasis on developing adaptive behavior and skills
- Sensitivity to the social and physical environment of the individual
- Thorough assessment prior to intervention to identify the relationship between a behavior and the environment in which it occurs
- An individualized treatment plan that is linked to the results of the assessment
- Clear identification of treatment goals
- Objective quantification of outcomes

Behavioral interventions are highly individualized and incorporate developmental, medical, situational factors, and caregiver (and when appropriate, client) perspective and needs in goal selection and treatment planning.

C.1 Literature search

For this review, articles describing the use of behavioral interventions with individuals with ASD under the age of five that were published between January 2000 and September 2011 were reviewed. Similar to the process employed for the 1999 ASD Guideline, the collection and review of articles was a three-step process involving an extensive literature search, a screening, and an in-depth review. Each of these steps is described in more detail below.

A search strategy was developed to identify relevant scientific research on behavioral interventions for children with ASD. For the purposes of this review, ASD was defined as Autistic Disorder, Pervasive Developmental Disorder – Not Otherwise Specified (PDDNOS) and Asperger's Disorder. Electronic searches were conducted using relevant computer bibliographic databases, which included MEDLINE (a database containing most of the medical literature and much of the psychological literature), PsycINFO, and ERIC. These were the same electronic databases used to collect literature for the 1999 ASD Guideline. The following search terms and search criteria were used in obtaining the articles is presented in C-16 below.

Table C-1.	General information on the search terms and constraints specified for search of bibliographic databases
Search terms	Autism, ASD, PDD-NOS, Behavioral Intervention, Behavior Modification, Behavior Therapy, Applied Behavior Analysis
Date Range	January 2000 – September 2011
Publication type	Peer Reviewed Journal
Publication language	English
Age	Infancy to 5 years

Additionally, reference lists of articles and reports reviewing the efficacy of behavioral interventions for individuals with ASD (AHRQ, 2011; Eikeseth, 2008; Eldevik, et al., 2009; Howlin, Magiati, & Charman, 2009; NAC, 2009) were manually searched in an attempt to identify studies that might have been missed in the electronic search.

C.2 Review Criteria

A total of 2,619 articles were found through the electronic and manual searches. Abstracts for all 2,619 articles were reviewed on the following criteria:

- Focused on a behavioral intervention (as defined above)
- Primary participants have an ASD
- Primary participants 5 years of age or younger

Articles that met the above criteria were obtained and included for screening. If it was unclear whether an article met criteria for screening based on the abstract, it was obtained and included for screening. Of the 2,619 articles reviewed, 374 met criteria for formal screening.

The 374 articles identified during the literature search were systematically screened to determine if they met criteria for in-depth review. A worksheet outlining the inclusion criteria for in-depth review was completed for each article.

Articles were divided among three independent raters, with training and education in psychology and ASD, for screening. Training on the operational definitions for each of the screening questions and focus categories was conducted and reliability was established prior to the start of screening. In addition, reliability checks were completed for 15% of all of the articles that were screened.

Following screening, 117 articles met criteria for in-depth review. Table C-2 provides a breakdown of those articles by study design and focus category.

Table C-2. Articles meeting criteria for in-depth review by focus category and design.		
Focus Area	Group	Single Subject
Academic	0	7
Anxiety	0	0
Behavior Reduction	0	16
Cognitive	0	0
Communication	8	27
Comprehensive	14	1
Daily Living	0	4
Feeding	0	1
Play	0	4
Sleep	0	2
Social	3	27
Toileting	0	3
Total Articles by Research Design	25	92
Grand Total of Articles for In Depth Review	117	

The 117 articles identified during the screening process were reviewed further to obtain information about the specific interventions being conducted and the outcomes for participants. A worksheet outlining all of the variables being collected for in-depth review was completed for each article.

The variables collected during in-depth review were based on the criteria used for the 1999 NYSDOH ASD Guideline and other published reports on evidence-based practices for individuals with ASD (NAC, 2009; AHRQ, 2011; Reichow, 2011). Variables were divided into two categories, article level and group level. Article level variables were those that pertained to the article (e.g., design, group assignment method). Group level variables were specific to the treatment group (e.g., number of hours of intervention per week, number of participants per group, outcome). Information on the article level and group level variables were collected using a standardized worksheet. Operational definitions were established for each of the variables and are shown in Table 3-18 below. Definitions for the variables were based on the 1999 ASD Guideline and other published reports on evidence-based practices for individuals with ASD (NAC, 2009; AHRQ, 2011; Reichow, 2011).

Table C-3. In-Depth Review Variable Definitions	
Number of Participants	The total number of participants in the study.
Age Range	The age range, in months, of all the participants in the study
Randomized	Was random assignment used to place participants into treatment groups? (Variable reported for studies using group design, only)
Group Type	Behavioral: See above definition. Eclectic: Group receiving intervention programs whose bases are drawn from multiple theoretical orientations. Non-Behavioral: Group receiving interventions whose bases are not behavioral. Control: Group not receiving the intervention under investigation to serve as a comparison to the treatment group. Participants in the control groups may be receiving treatment as usual in the community or no treatment at all.
Number of Participants	The number of participants in the treatment group.
Behavioral Intervention Type	Variable only completed for those interventions that were marked as "behavioral" for the "group type." Comprehensive: This treatment encompasses programs that involve a combination of applied behavior analytic procedures (e.g., discrete trial, incidental teaching, etc.), which are delivered to young children (generally under the age of 8). These treatments may be delivered in a variety of settings (e.g., home, self-contained classroom, inclusive classroom, community) and involve a low student-to-teacher ratio (e.g., 1:1). These treatments generally have the following characteristics {a} target the defining symptoms of ASD {b} have treatment manuals, {c} providing treatment with a high degree of intensity, and {d} measure the overall effectiveness of the program. Early Start Denver Model: Comprehensive behavioral treatment model developed by Rogers & Dawson (Rogers, S. The Early Start Denver Model. In Romancyzk, R.G., and McEachin (EDS) (2016). Comprehensive Models of Autism Spectrum Disorder Treatment: Points of Divergence and Convergence. Springer, ISBN: 978-3-319-30903-0). Lovaas: Comprehensive behavioral treatment model developed by Lovaas (Leaf, R. & McEachin, J. (2014). The Lovaas Model. In Romanczyk, R.G., and McEachin (Eds), (2016). Comprehensive Models of Autism Spectrum Disorder Treatment: Points of Divergence and Convergence. Springer, ISBN: 978-3-319-40903-0. Behavioral Component: Interventions focused on evaluating the effect of specific behavioral strategies such as prompting, modeling, fading, and reinforcement. Parent Training: Studies focused specifically on evaluating the efficacy of programs designed to teach parents to implement treatment protocols. Peer Training: Studies focused specifically on evaluating the efficacy of

Table C-3. In-Depth Review Variable Definitions	
	programs designed to teach peers to implement treatment protocols. TEACCH: Behavioral treatment model developed by Schopler (Gary B. Mesibov; Victoria Shea; Eric Schopler. (2004). The TEACCH Approach to Autism Spectrum Disorders. Springer. ISBN 978-0-306-48646-3.). Other: Behavioral treatments that did not fit in any of the other behavioral categories. Some of the treatments included in this category were the Picture Exchange Communication System (PECS) Bondy AS, Frost LA (1994). The Picture Exchange Communication System. Focus on Autism and Other Developmental Disabilities, Vol. 9, No. 3, 1-19 (1994), Pivotal Response Treatment (PRT) (Koegel, Robert L. & Lynn Kern Koegel (c. 2006)). Pivotal Response Treatments for Autism: Communication, Social, and Academic Development. Baltimore, Md.: Paul H. Brookes. ISBN 1-55766-819-1., and functional communication training (FCT) (Tiger, J., Hanley, G., & Bruzek, J. (2008). Functional Communication Training: A Review and Practical Guide. Behavior Analysis in Practice. Spring; 1(1): 16–23.
Group Description	Name of group and one or two other relevant descriptors.
Intervention Focus	The specific goals or foci of the intervention (e.g., reduce repetitive behavior, increase number of sight words).
Diagnosis	The diagnoses represented in the treatment group.
Hours Per Week	The range of hours per week each participant received the intervention.
Age Range	The age range, in months, for the participants in the treatment group.
Results	Significantly Improved: Statistically significant positive changes observed in participant behaviors and scores on standardized assessments following intervention. Improved: Some statistically significant positive changes may have been observed in participant behaviors and scores on standardized assessments; however, the changes were not consistent across all measures or changes may not have been maintained at follow up. No Change: No significant changes observed in participant behavior or assessment scores following intervention. Worse: Some participant behaviors and scores on standardized measures were worse following intervention. Significantly Worse: Statistically significant negative changes observed in participant behaviors and scores on standardized assessments following intervention.

Articles were divided among three independent raters, with training and education in psychology and ASD, for screening. Training on the operational definitions for each of the screening questions and focus categories was conducted and reliability was established prior to the start of screening. In addition, reliability checks were completed for 15% of all the articles that were screened.

C.3 Results of Review

The results of the review are described in the figures and tables below.

Table C-4. Articles meeting criteria for in-depth review by study design (N=117)		
Study Design	**Number of Articles**	**Percentage**
Group Design	25	22%
Single Subject	92	78%

Figure 1 displays the increase in the total number of articles meeting criteria for in-depth review published between 2000 and 2011 (n=117) compared with the number reviewed for the 1999 ASD Guideline (n=27), for both single subject and group design studies.

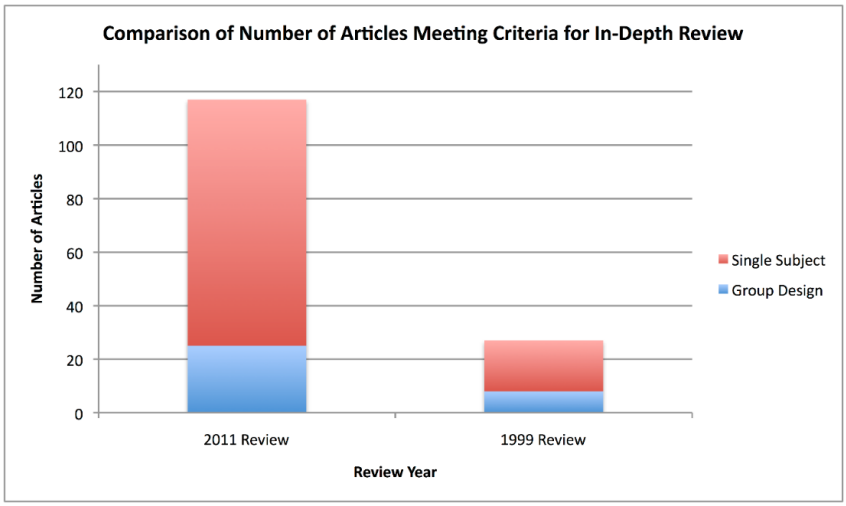


Figure 2 illustrates the increase in the number of studies with participants from birth through five years of age in studies selected for in-depth review published between 2000 and 2011 (n=117) compared with studies with participants in this age range reviewed for the 1999 ASD Guideline (n=27).

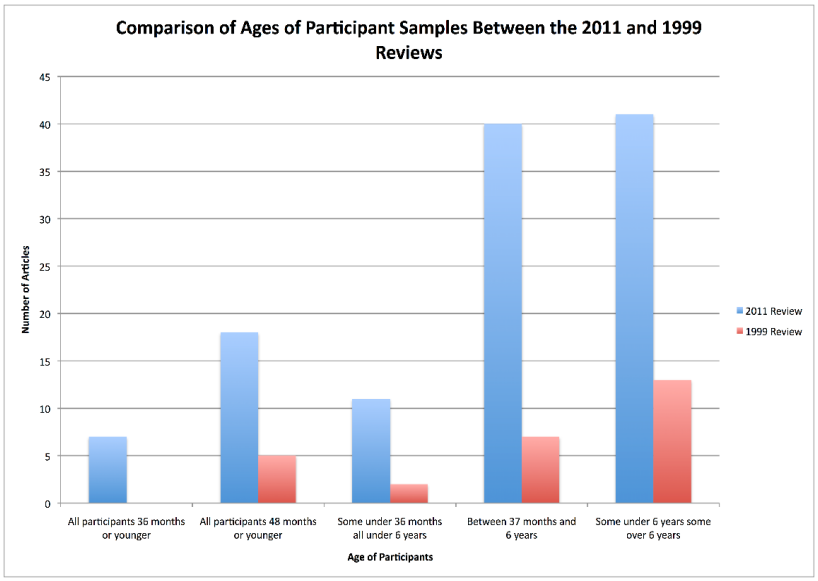


Table C-5. Group assignment methods		
Group Assignment	**Number of Articles***	**Percentage**
Random	11	44%
Non-Random	14	56%
** Only articles utilizing a group design were included in these analyses.*		

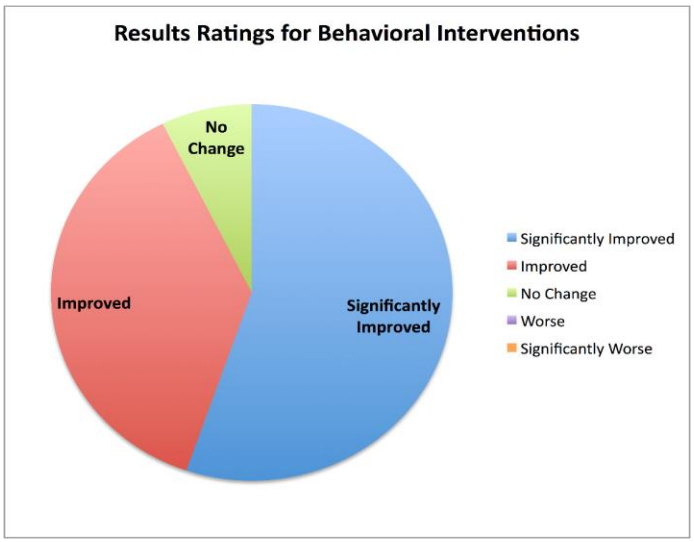
Table C-6. Age demographics for participant samples		
Age of Participants	**# of Articles**	**Percentage**
All participants 36 months or younger	7	6%
All participants 48 months or younger	18	15%
Some participants under 36 months, all under 6 years	11	9%
All participants between 37 months and 6 years	40	34%
Some under 6 years, some over 6 years	41	35%

Table C-7. Race demographics for participant samples		
Race	**Number of Articles**	**Percentage**
Race Info Reported	32	27%
No Race Info Reported	85	73%
	Number of Articles*	**Percentage****
American Indian or Alaska Native	1	3%
Asian	16	50%
Black or African American	14	44%
Native Hawaiian or Other Pacific Islander	0	0%
White	29	91%
** The number of articles with at least one individual of that race represented in the sample* *** Of those that reported information on participant race, the percentage of studies containing at least one participant from a race category*		

Table C-8. Ethnicity demographics for participant samples		
Ethnicity	**Number of Articles**	**Percentage**
Ethnicity Info Reported	26	22%
No Ethnicity Info Reported	91	78%
	Number of Articles*	**Percentage****
Hispanic or Latino	12	46%
Not Hispanic or Latino	26	100%
** Number with at least one individual of that ethnic group represented in the sample* *** Of those with reported information ethnicity, percent with at least one participant the category*		

Table C-9 Behavioral intervention type		
	# of Articles	**Percentage**
Comprehensive	3	2%
Early Start Denver Model (ESDM)	3	2%
Lovaas	10	8%
Behavioral Component	82	67%
Parent Training	4	3%
Peer Training	1	1%
TEACCH	3	2%
Other	15	12%

Figure 3. Outcome improvement ratings for reviewed studies



C.4 Conclusion of Review

The purpose of this review was to acquire and review (using the 1999 ASD Guidelines methodology) the empirical literature on the use of behavioral interventions with individuals with ASD ages birth to 5 years published between 2000 and 2011. The majority of the studies identified (78%) were single subject design and 22% were group designs. Of these group designs, 44% employed a randomized group assignment methodology. Communication and social skills were the most common focus area for interventions and more than half of the articles on behavioral interventions reported significant improvements.

Report of Research for Interventions for Children with Autism Spectrum Disorders

An Analysis of Published Research Evaluating Outcomes Associated with Parent-Mediated Interventions for Young Children with ASD: Years 1999-2013

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D. Parent-Mediated Interventions

The purpose of this review was to acquire and review the empirical literature evaluating the efficacy of parent-mediated intervention approaches for young children with ASD. Parent-mediated interventions were defined broadly as interventions where parents are responsible for carrying out some or all of the intervention with their own child (Wong et al., 2013). This definition includes interventions aiming to improve parent cognitions and emotions (e.g., parenting stress) that are closely related to parenting practices. Throughout this summary, these interventions are referred to as parent-mediated, although a range of other labels can be found in the literature (e.g., parent training, parent education, parent-implemented intervention, parent coaching).

D.1. Literature search

For this review, articles evaluating parent-mediated interventions in samples of children with ASD (6 years or younger) that were published between January 1999 and December 2013 were reviewed. Similar to the process employed by the 1999 NYSDOH ASD Guideline Guidelines, the procedures for acquiring and reviewing the existent literature included three steps: 1) computerized bibliography searches, 2) systematic screening of article abstracts, and 3) in-depth review of full articles. The procedures for, and results from each step are described in detail below.

A search strategy was developed to identify relevant scientific research on parent-mediated interventions for children with ASD. The bibliographic databases included in the electronic searches included MEDLINE, PsycINFO, ERIC, PubMed, Web of Science, Social Work Abstracts, CINAHL, Sociological Abstracts, and SOCIndex. The general search terms and constraints used for searching the electronic databases (with slight modifications depending on the database search functions) are presented in Table D-1. Please note that the search terms/constraints for the other databases were modified slightly due to differences in the databases' available search functions. After removing duplicate entries from the search results, a total of 5,380 unique articles were identified.

Table D-1. Terms and specified constraints for search of bibliographic databases.

Boolean search expression	(autistic OR autism OR asd OR pervasive development OR pervasive developmental OR pdd OR asperger OR asperger's OR aspergers OR hfa [Title Word or Abstract Word]) AND (intervention OR treatment OR practice OR strategy OR therapy OR program OR procedure OR education OR training OR therapeutics OR teaching OR psychotherapy OR behavior modification OR instruction OR instructional [Title Word or Abstract Word]) AND (parent OR mother OR father OR caregiver [Title Word or Abstract Word])
Date of Publication	1999 to 2013

Table D-1. Terms and specified constraints for search of bibliographic databases.	
Publication type	Peer Reviewed Journal
Publication language	English
Age	Childhood (birth-12 yrs); Neonatal (birth-1mo); Infancy (2-23 mos); Preschool Age (2-5 yrs); School Age (6 -12)

Note. Due to differences in available search functions, search terms and constraints were adapted slightly for each bibliographic database.

Abstracts obtained from computerized bibliography searches were screened using four criteria. First, is the study evaluating a program or intervention where parents are responsible for carrying out all or some of the intervention with their own child? This included interventions that aimed to improve parent cognitions and emotions (e.g., parenting stress) that are closely related to parenting practices. Second, does the study provide original data about the efficacy of the intervention method (i.e., not a systematic review)? Third, do the primary participants have ASD (at least some individuals identifying as having an ASD)? Fourth, are the primary participants 6 years of age or younger (at least one individual that is 6 years or younger)? Any article that failed to meet one or more of these four criteria was dropped from further consideration. However, abstracts that provided insufficient information for evaluating these criteria were selected for full-text review. Based on this screening process, we selected 310 articles for full-text review.

Inter-rater agreement on the decision to select or drop an article was evaluated using a second reviewer, who independently reviewed 676 (13%) of the screened abstracts. Since the true threat to the integrity of the selection process lies in the possibility that our primary coder erroneously failed to select an article for full-text review (as compared to erroneously selecting an article for full-text review that should have been dropped), a weighted Kappa coefficient was calculated to evaluate the reliability of the coding procedures. Results revealed excellent inter-rater reliability, $Kappa_w = .92$.

The full texts of all 310 articles that were selected for full-text review were obtained. In addition, the reference lists of review articles and reports were manually reviewed in an attempt to identify studies that might have been missed in the electronic search (e.g., Boyd, Odom, Humphreys, & Sam, 2010; Eldevik et al., 2009; Hoagwood, 2005; Howlin, Magiati, & Charman, 2009; McConachie & Diggle, 2007; Woods & Wetherby, 2003; Wong, et al., 2013). This manual search yielded an additional 9 articles. The full-text of the resulting 319 articles was evaluated in two sub-steps: (1) Full-text review using a standard evaluation criteria, and (2) Full-text review to determine final selection of articles.

D.2. Selecting articles for review

The full-text of all 319 articles was evaluated using criteria developed by the 1999 NYSDOH ASD Guideline panel. These criteria were intended to specify minimum quality and applicability standards for providing adequate evidence about the efficacy of the evaluated intervention approach. Details on these evaluation criteria are provided in Table C-26. Any article that failed

to meet one or more of these evaluation criteria was dropped from further consideration. In applying these evaluation criteria, we selected 140 articles for further consideration.

Table D-2. Standard evaluation criteria for full-text review

Criterion	Description
General Requirements	
1	Is the study published in English in a peer-reviewed scientific/academic publication?
2	Does the study provide original data about the efficacy of an intervention method for ASD?
3	Does the study evaluate a parent-implemented intervention (i.e., a program/intervention where parents are responsible for carrying out all or some of the intervention with their own child)?
4	Does the study provide adequate description of the intervention method evaluated, or provide a reference where such a description could be found?
5	Does the study evaluate functional outcomes that are important to a child's overall health or development or are important for the family or society?
6	Does the study evaluate children with ASD of appropriate age (at least one child with ASD who is 6 years or younger)?
Group Design Requirements (criteria used for group designs only)	
7	Is the study a controlled trial evaluating a group receiving the intervention compared to a group(s) receiving no intervention or a different intervention?
8	Does the study assign participants to groups either randomly or using a method that does not appear to significantly bias results?
9	Does the study use equivalent methods for measuring baseline participant characteristics and outcomes for all groups studied?
Single-Subject Design Requirements (criteria used for single-subject designs only)	
10	Does the study report on at least 3 participants?
11	Does the study use an acceptable single-subject research design (details specified in the 1999 ASD Guideline)?

Note: Unless otherwise specified, these criteria were developed by the 1999 NYSDOH ASD Guideline panel. Criteria #3 was added to reflect the current projects' focus on parent-mediated interventions. One additional criteria developed by the 1999 NYSDOH ASD Guideline panel was not implemented in the current review (Did the study evaluate an intervention method that is not currently available to providers in the U.S.?). If reviewers were unsure as to whether these criteria were met, they were instructed to select the article for further consideration.

Like the previous review step, inter-rater agreement on the decision to select or drop an article was evaluated using one reviewer as the "gold standard coder," who independently reviewed

70 (22%) of the evaluated full-text articles. Results revealed excellent inter-rater reliability, $Kappa_w = .87$. All articles nominated to be dropped during this step were independently reviewed by the principal investigator of the review.

The full texts of all articles selected during the selection step was reviewed by the lead investigator of the evidence review and at least one additional reviewer. The purpose of this review step was to complete a detailed review of the study design, the nature of the intervention, participant characteristics, outcome measures, and results. Based on these detailed reviews, an additional 65 articles were dropped. The decision to keep or drop an article during this follow up was based on consensus between two or more reviewers. The reasons for dropping articles during this step are presented in Table D-3. The remaining 75 articles were considered to provide adequate evidence about the efficacy of a parent-mediated intervention for young children with ASD.

Table D-3. Reasons for dropping articles in the second review process.

Reasons	Description
The research design does not adequately isolate the parent-mediated intervention component (30 articles dropped)	Conclusions about the efficacy of a parent-mediated intervention are not possible, either because the parent-mediated intervention was merely a component of a more comprehensive intervention program (26 articles), or because the parent-mediated intervention was evaluated in comparison to a more intense interventionist-delivered intervention (4 articles).
The research design does not meet the minimum standards established by the 1999 ASD Guidelines for either a 'controlled group design' or a 'single- subject design' (20 articles dropped)	These were either pre-post group designs without an adequate control group, or case reports that did not use adequate single-subject methodology.
Children were older than 6 years (6 articles dropped)	Group studies with a mean chronological age of 8 years or above were excluded, even if the youngest child was 6 years or younger.
Sample size < 3 (4 articles dropped)	After detailed review, the sample size was determined to be inadequate.
The article appeared in print in 2014 (3 articles dropped)	The reviewed article was an advance online publication.
The article evaluated the efficacy of a parent support group (2 articles dropped)	Articles evaluating the efficacy of parent support groups were not included.

D.3 Results of research review

A total of 75 articles met criteria for providing evidence about the efficacy/effectiveness of parent-mediated interventions for young children with ASD. These 75 articles reported on the results of 69 research studies. Findings from three controlled group studies were published as multiple articles. For example, results from the clinical trial conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network were published in five separate articles

(Aman et al., 2009; Arnold et al., 2012; Farmer et al., 2012; Handen et al., 2013; Scahill et al., 2012). Similarly, results from a pilot study providing evidence for the subsequent Preschool Autism Communication Trial (PACT; Aldred et al., 2004; Aldred et al., 2012) were published as two separate articles. Finally, results from a clinical trial evaluating the efficacy of a combined home-based (i.e., parent-mediated) and center-based program, compared to a center-based program only, were published as two separate articles (Rickards et al., 2007; Rickards et al., 2009).

Evidence tables tabulating summary information were prepared and provided to the panel for each article (e.g., research design, type of control, sample size, participant age, intervention type, intervention intensity, intervention focus, and the country where the research was completed). Evidence tables for all selected articles are available on request. One article used a combination of a single-subject and a controlled group design (Welterlin et al., 2012). Since the most relevant findings from this study were based on the single-subject analysis, this article is classified accordingly. The following graphs and tables describe and compare the 69 research studies, or 75 research articles, that met criteria for providing evidence about the efficacy/effectiveness of parent-mediated interventions for young children with ASD.

Research design and intervention focus

Data on the studies' research design and intervention focus are presented in Table D-4. Results show that 38 studies (55%) used a single-subject design, 26 studies (38%) used a randomized controlled group design, and 5 studies (7%) used a quasi-experimental group design. Moreover, the majority of evaluated interventions (46 studies, 67%) focused on outcomes related to children's social/ communication skills.

Table D-4. Results on study research design and intervention focus

	Single-Subject Design	Quasi-Experimental Group Design	Single-Site Randomized Controlled Trial	Multi-Site Randomized Controlled Trial	Sum
Focus Category					
A. Social/Communication	28	3	11	4	46
B. Behavior reduction	6	-	3	1	10
C. Parent knowledge & well-being	-	2	4	-	6
D. Sleep	1	-	1	1	3
E. Academic	1	-	1	-	2
F. Feeding	1	-	-	-	1
G. Toileting	1	-	-	-	1
Sum	38	5	20	6	69

Number of research articles by publication year

Results in the number of research articles by publication year and research design indicate a steep increase in research publications since 2010. That is, 24 (65%) out of 37 research articles using a controlled group design were published since 2010. Similarly, 17 (45%) out of 38 research articles using a single-subject design were published since 2010.

Age of child participants

Information on the age of the children participating in the 69 research studies is presented in Table D-5. Results show that only 10 intervention studies (14%) enrolled exclusively children younger than 36 months. Twenty-three intervention studies (33%) enrolled exclusively children younger than 48 months.

Table D-5. Numbers of studies (N = 69) by child age and research design

	Single-Subject Design	Controlled Group Design	Sum
All participants 36 months or younger	5	5	10
All participants 48 months or younger	9	4	13
Some participants under 36 months, all under 6 years	7	6	13
All participants between 37 months and 6 years	4	6	11
Some under 6 years, some over 6 years	13	9	22
Insufficient information provided	0	1	1

Country where the research was conducted

Table D-6 presents information on the countries where the intervention research was conducted. Out of the 69 selected intervention studies, 48 (70%) were completed in the U.S. Reporting on the families' ethnic/racial origin was inconsistent for single-subject research, however controlled group studies completed in the U.S. enrolled on average 38% families belonging to an ethnic/racial minority, with studies ranging from 18% to 80%.

Table D-6. Numbers of studies (N = 69) by country of research completion

	Single-Subject Design	Controlled Group Design	Sum
United States	33	15	48

Table D-6. Numbers of studies (N = 69) by country of research completion			
	Single-Subject Design	Controlled Group Design	Sum
Australia	1	5	6
Canada	3	1	4
United Kingdom	0	4	4
Thailand	0	2	2
China	0	1	**1**
India	0	1	**1**
Japan	0	1	**1**
Netherlands	0	1	**1**
Turkey	1	0	**1**

Note. On average, families enrolled in controlled group studies conducted in the U.S. were 38% minority (e.g., Hispanic, Black, Asian), with studies ranging from 18% to 80%.

Sample size

Table D-7 presents information on the samples sizes of the 69 selected research studies. Twenty- two single-subject studies (58%) were based on only 3 participants, while ten single-subject studies (26%) enrolled more than 5 participants. In contrast, the median sample size of controlled group studies was 39 participants, with studies ranging between 14 and 152 participants.

Table D-7. Numbers of studies (N = 69) by sample size			
	Single-Subject Design	Controlled Group Design	Sum
3 participants	22	-	22
4-5 participants	6	-	6
6-10 participants	9	-	9
11-20 participants	1	2	3
21-30 participants	-	8	8
31-40 participants	-	7	7
41-60 participants	-	4	4

Table D-7. Numbers of studies (N = 69) by sample size			
61-80 participants	-	6	6
81-120 participants	-	2	2
121-160 participants	-	2	2

Type and model of interventions studied

Table D-8 presents information on the type or model of interventions studied. Results show that almost half of the selected studies (48%) evaluated behavioral or developmental interventions methods. The intervention method that was evaluated most frequently (9 studies, 13%) was Pivotal Response Training, followed by 4 studies (6%) evaluating the Early Start Denver Model.

Table D-8. Numbers of studies (N = 69) by intervention type			
	Single-Subject Design	Controlled Group Design	Sum
Behavioral/ Developmental Intervention Approach model	14	19	33
Pivotal Response Training	8	1	9
Early Start Denver Model	3	1	4
Hanen More Than Words	0	3	3
Functional Communication Training	3	0	3
Augmentative & Alternative Communication (e.g., PECS)	3	0	3
Project ImPACT/ Reciprocal Imitation Training	3	0	3
DIR/Floortime	0	2	2
Enhanced Milieu Teaching	1	1	2
Stepping Stones Triple P	0	2	2
Mindfulness-Based Parent Training	1	1	2
TEACCH	1	0	1
Incidental Teaching	1	0	1
Massage Therapy	0	1	1

D.4 Conclusion of Review

In the past two decades, there has been an increasing number of studies which focus on promoting social communication development in infants and toddlers at risk or with ASD. This includes an increase in studies on parent-mediated interventions approaches that aim to increase the capacity of families to meet the complex needs of young children with ASD (Wetherby & Woods, 2008). The purpose of the current review was to acquire and review the published literature evaluating the efficacy/effectiveness of parent-mediated interventions in samples of children with ASD (6 years or younger) that were published between January 1999 and December 2013. Following an extensive literature search, screening, and evaluation process, 75 peer-reviewed journal articles were identified that met minimum quality and applicability standards for studies providing adequate evidence about the efficacy of the evaluated interventions. The identified research articles reported on the results of 69 unique research studies. About half of the studies (55%) used a single-subject design, with the remaining studies using controlled group designs. The majority of the evaluated interventions (67%) focused on improving children's social and communication skills.

Report of Research for Interventions for Children with Autism Spectrum Disorders

An Analysis of Published Research on ABA-Based Early Intensive Behavioral and Developmental Approaches: 2013-2015

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E. Behavioral/Developmental Interventions: Update of AHRQ Reviews

In 2011 and 2014, the Agency for Healthcare Research and Quality (AHRQ) published a pair of systematic literature reviews of interventions for children with Autism Spectrum Disorder (ASD): 2011 AHRQ Report (Warren et al., 2011) and 2014 AHRQ Report (Weitlauf et al., 2014). These literature reviews were completed by the Vanderbilt Evidence-based Practice Center, and incorporate literature published between 2000 and 2013. The methodology that guided the 2011 and 2014 AHRQ reports is similar to the methodology that guided the 1999 NYSDOH ASD Guideline (i.e., bibliographic search and literature retrieval; selection of studies using established criteria; analysis of scientific evidence; and, development of evidence tables to summarize information about the selected studies).

Despite these overall similarities, two important differences are worth noting. The 2014 AHRQ Report considered only controlled group designs (e.g., randomized controlled trials, prospective and retrospective cohort studies, and nonrandomized controlled trials). In addition, the 2011 and 2014 AHRQ Reports differ from each other in another way. The 2011 AHRQ Report covered a broad range of Behavioral Interventions (e.g., early intensive behavioral & developmental, social skills, play-/interaction-based, interventions targeting associate behaviors), Educational Interventions (i.e., Treatment and Education of Autistic and Communication related handicapped CHildren [TEACCH], broad-based approaches, computer-based approaches), and Allied Health Interventions (e.g. language therapy, sensory, auditory/music therapy). In contrast, the 2014 AHRQ Report focused exclusively on behavioral interventions.

Table E-1 Comparison of AHRQ reviews – 2011 vs. 2014		
	2011 AHRQ *(2000-2010)*	2014 AHRQ *(2010-2013)*
Behavioral Intervention Studies	45 (29 RCTs)	65 (48 RCTs)
Educational Intervention Studies	10 (3 RCTs)	
Allied Health Intervention Studies	9 (7 RCTs)	
Other Intervention Studies	1 (1 RCT)	

The purpose of the current review is to acquire and review the empirical intervention literature published since the review-deadline for the 2014 AHRQ Report (December 2013). To allow for some delays in the database-indexing of journal articles (PsycINFO, ERIC, PUBMED), we reviewed literature published in 2012 and thereafter. The methodology used for the current literature review was based on the methodology outlined in 2014 AHRQ Report. Thus, only research that used a controlled group design (i.e., quasi-experiments, randomized controlled trials) was considered to provide adequate evidence about the efficacy/effectiveness of the evaluated intervention. However, in contrast to the 2014 AHRQ Report, the current literature review only included samples of children 6 years and under. The procedures for acquiring and reviewing the existing literature included three steps: 1) computerized bibliography searches, 2) systematic screening of article abstracts, and 3) in-depth review of full articles.

E.1 Search of Bibliographic Databases and Abstract Review

A search strategy was developed to identify relevant scientific research on interventions for children with ASD. Consistent with the 2014 AHRQ Report, the bibliographic databases included in our electronic searches were PsycINFO, ERIC, and PubMed. The terms and constraints used to search these bibliographic databases were similar to the ones used for the 2014 AHRQ Report. Final electronic searches were completed in 2015. Search results from all electronic databases were managed in EndNote, a commercial reference management software package produced by Thomson Reuters. After removing duplicate entries, a total of 4,631 unique articles were identified (1005, 1190, 1315, and 1121 articles published in 2012, 2013, 2014, and 2015, respectively).

Abstracts obtained from computerized bibliography searches were screened using the five criteria specified in Table E-2. These screening criteria were identical to the criteria used in the 2014 AHRQ Report, with the exception that our search criteria only identified primary research studies (the 2014 AHRQ Report also identified systematic research reviews and meta-analyses). Any article that failed to meet one or more of these five criteria was dropped from further consideration. Based on this screening process, we selected 430 articles for full-text review (84, 101, 131, and 114 articles were published in 2012, 2013, 2014, and 2015, respectively).

Table E-2. Criteria for systematic screening of article abstracts

X1	Addresses intervention approach and outcomes for young children (0-12 years) with ASD or at risk for ASD.
X2	Is a primary research study (no research reviews or meta-analyses).
X3	Includes individuals with ASD in target age range (0-12 years).
X4	Addresses one of the following: • Treatment modality for ASD intended to modify core symptoms of ASD in individual diagnosed/at risk • Short or long term outcomes of treatment intended to modify core symptoms/co-morbidities of ASD in individual diagnosed/at risk; outcomes include parent and child quality of life • Modifiers of treatment outcomes in young children with ASD • Generalization of treatment outcomes to another person/context • Drivers of treatment outcomes • Harms/adverse effects associated with treatment intended to modify core symptoms of ASD in individual diagnosed/at risk
X5	Eligible study size (at least 10 total participants)
Note: Abstracts that provided insufficient information for evaluating these criteria were selected for full-text review.	

Full-text Review to Identify Articles Providing Adequate Evidence

Articles selected for full-text review were evaluated using the eight criteria specified in Table E-3. Criteria Y1-Y4 and Y6-Y7 were directly derived from the 2014 AHRQ Report (with the exception that we did not include research reviews and meta-analyses). Criteria Y5 considered the full range of Behavioral Interventions, Educational Interventions, and Allied Health Interventions covered in the 2011 AHRQ Report (pp. 1-12; Warren et al., 2011). Criteria Y8 (study includes participants 6 years and younger) was added to be consistent with the

methodology used by the 1999 NYSDOH ASD Guideline. Based on these evaluation criteria, a total of 257 articles failed to meet at least one of criteria Y1-Y7 (i.e., the inclusion criteria specified in the 2011 and 2014 AHRQ Reports). In addition, 92 articles failed to meet the revised age cutoff (Y8). Finally, 5 studies were removed due to grave flaws in research methodology (e.g., cursory description of the intervention methods, inadequate design or analysis) (Reitzel et al., 2013; Samadi & Mahmoodizadeh, 2014; Sandiford, Mainess, & Daher, 2013; Strauss et al., 2015; Strauss et al., 2014).

A total of 76 articles met criteria for providing adequate evidence about the efficacy and/or effectiveness of an intervention approach for young children with ASD. Out of those 76 articles, 27 were previously included in the 2014 AHRQ Report. The remaining 49 articles reported on 47 unique research studies. For 6 of these 47 unique research studies, previous publications on the same study were identified (Carter et al., 2011; Casenhiser, Shanker, & Stieben, 2013; Dawson et al., 2012; Dawson et al., 2010; Green et al., 2010; Kasari, Freeman, & Paparella, 2006; Kasari, Gulsrud, Freeman, Paparella, & Hellemann, 2012; Kasari, Paparella, Freeman, & Jahromi, 2008; Siller, Hutman, & Sigman, 2013; Yoder & Stone, 2006a, 2006b). When preparing the evidence tables for these 6 studies, previous publications were incorporated. In summary, we created evidence tables for 47 unique studies, reported in 61 peer-reviewed articles.

Table E-3. Criteria for systematic full-text review of article	
Y1	Includes participants ages 2-12 (mean age + SD ≤ 12 years 11 months) diagnosed with ASD or 0-2 at risk for ASD diagnosis (or: 80% of the participants with ASD/at risk for ASD were in the 0 to 12 age range).
Y2	Is a primary research study (no research reviews or meta-analyses).
Y3	Includes at least 10 individuals with ASD (or at risk) in the target age range. If the study includes individuals with ASD and those with other developmental disabilities, data for the participants with ASD could be isolated.
Y4	Addresses one of the following: • Treatment modality for ASD intended to modify core symptoms of ASD in individual diagnosed/at risk • Short or long term outcomes of treatment intended to modify core symptoms/co-morbidities of ASD in individual diagnosed/at risk; outcomes include parent and child quality of life • Modifiers of treatment outcomes in young children with ASD • Generalization of treatment outcomes to another person/context • Drivers of treatment outcomes • Harms/adverse effects associated with treatment intended to modify core symptoms of ASD in individual diagnosed/at risk
Y5	Evaluates intervention approaches. INCLUDED are intensive behavioral and developmental interventions, social skills interventions, parent training, play/interaction focused approaches, interventions targeting symptoms commonly associated with ASD such as anxiety, and other general psychosocial approaches. Included are also educational interventions (e.g., center-based programs, TEACCH) and allied health interventions (interventions typically provided by speech/language, occupational: PECS, Responsive Education and Prelinguistic Milieu Teaching, Sensory Integration, animal assisted interventions). EXCLUDED are primarily medical and related interventions (e.g., antipsychotics, SRI, stimulants, dietary supplements/restrictive diets), physical education

Table E-3. Criteria for systematic full-text review of article	
	procedures, complementary or alternative interventions (e.g., acupuncture), and parent self-help groups.
Y6	Y6(x): The study used a comparative design (any study that included both a treatment/intervention and a separate control group).
Y7	Y7(x): Full-text article not obtainable
Y8	Y8(x): Includes participants ages 2-6 (mean age + SD ≤ 6 years 11 months) diagnosed with ASD or 0-2 at risk for ASD diagnosis (or: 80% of the participants with ASD/at risk for ASD were in the 0 to 6 age range).
Note: Abstracts that provided insufficient information for evaluating these criteria were selected for full-text review.	

To evaluate the inter-rater reliability of our procedures for implementing the bibliographic searches, screening of article abstracts, and full-text review, all articles published in 2012 were used to compare the results of the current review to the results of the 2014 AHRQ Review (given delays in the database-indexing of journal articles, articles published in 2012 were only partially reviewed in the 2014 AHRQ Review). Overall, the bibliographic search strategy used in the current report was more inclusive than the search strategy used in the 2014 AHRQ Report. In addition, the inter-rater agreement for screening and article selections was excellent (kappa = .89).

E.2 Results of the Research Review

This review of the intervention literature published since January 2012 identified 47 unique research studies that met criteria for adequate evidence about an intervention approach for young children with ASD. The results of these 47 research studies were reported in 61 peer-reviewed research articles.

Evidence tables were prepared to tabulates summary information for each article (e.g., intervention context, research design, type of control, sample size, participant age, intervention brand/type, intervention intensity, intervention focus, mode of intervention delivery, and the country where the research was completed). Evidence tables are available on request and present the completed evidence tables for the 47 selected research studies. Evidence tables are organized hierarchically by (1) intervention context (i.e., parent, individual, classroom), and (2) intervention focus (i.e., comprehensive, social-communication & language focus, infant risk markers, parent knowledge & well-being focus, sensory-regulation, behavior reduction, sleep, peer-interaction). The following graphs and tables briefly describe and compare the 47 research studies that met criteria for providing evidence about the efficacy/effectiveness of an intervention approach for young children with ASD.

Research design and intervention focus

Data on the studies' intervention context (i.e., parent, individual classroom), research design (i.e., Quasi-Experiment, Randomized Controlled Trial), and intervention focus category are presented in Table E-4. Results show that 31 studies (66%) reported on a Randomized Controlled Trial, while 16 studies used a Quasi-Experimental design. Results also showed that 31 studies (66%) evaluated parent-mediated interventions, while 11 (23%) and 5 (11%) studies were implemented individually or in a classroom context, respectively.

Table E-4. Number of studies (Total N = 47), by intervention context, design (Quasi-Experiment (Q-E), Randomized Controlled Trial (RCT), and intervention focus							
Focus Category	Parent		Individual		Classroom		Sum
Design	Q-E	RCT	Q-E	RCT	Q-E	RCT	
A. Comprehensive	0	6	2	1	4	0	13
B. Social-communication &	2	10	3	3	0	0	18
C. Infant risk markers	2	2	0	0	0	0	4
D. Parent knowledge & well-being	1	2	0	0	0	0	3
E. Sensory-regulation	1	2	1	1	0	0	5
F. Behavior reduction	0	2	0	0	0	0	2
G. Sleep	0	1	0	0	0	0	1
H. Peer-interaction	0	0	0	0	0	1	1
Sum	6	25	6	5	4	1	47

Age of child participants

Information on the average age of the children participating in each of the 47 research studies is presented in Table E-5. Results show that 14 studies (30%) evaluated interventions that were delivered to groups of children that were on average 36 months or younger.

Table E-5. Number of studies (Total N = 47) by design and mean chronological age of children in the intervention group				
	Quasi-Experiment	**Single-site Randomized Controlled Trial**	**Multi-site Randomized Controlled Trial**	**Sum**
0 – 15 months	2	1	1	**4**
16 – 24 months	0	1	3	**4**
25-36 months	2	4	0	**6**
37-48 months	7	7	2	**16**
49-60 months	3	8	2	**13**
61-80 months	1	0	1	**2**
Note: Two studies did not report the mean chronological age of their intervention sample				

Sample size

Table E-6 presents information on the samples sizes of the 47 selected research studies (i.e., reported are the sample sizes of the groups receiving the experimental intervention). Twenty-nine of the published research studies (72%) had samples that included at least 20 participants in the experimental group.

Table E-6. Numbers of studies (Total N = 47) by design and sample size				
	Quasi-Experiment	**Single-site Randomized Controlled Trial**	**Multi-site Randomized Controlled Trial**	**Sum**
0-10 participants	5	2	0	7
11-20 participants	6	5	0	11
21-30 participants	3	5	1	9
31-40 participants	0	5	2	7
41-60 participants	1	3	4	8
61-80 participants	0	0	2	2
81-120 participants	1	1	1	3

Country where the research was conducted

Table E-7 presents information on the countries where the intervention research was conducted. Out of the 47 selected intervention studies, 29 (62%) were completed in the U.S. The remaining 18 studies were conducted across 10 different countries, including the United Kingdom, Australia, and Japan.

Table E-7. Numbers of studies (Total N = 47) and country				
	Quasi-Experiment	**Single-site Randomized Controlled Trial**	**Multi-site Randomized Controlled Trial**	**Sum**
U.S.	**8**	**13**	**8**	**29**
AUS	**1**	**2**	**0**	**3**
Canada	**1**	**1**	**0**	**2**
U.K.	**1**	**1**	**2**	**4**
Thailand	**1**	**0**	**0**	**1**
China	**1**	**0**	**0**	**1**
Japan	**1**	**2**	**0**	**3**
Netherlands	**0**	**1**	**0**	**1**
Belgium	**1**	**0**	**0**	**1**
Italy	**1**	**0**	**0**	**1**
Norway	**0**	**1**	**0**	**1**

Study Quality Assessment

The methodological rigor of each study was assessed by assigning points based on the following criteria: Study design (2 pts.); Diagnostic Approach (2 pts.); Participant Ascertainment (2 pts.); Intervention (2 pts.); Outcome Measurement (1 pt.) and Analysis Approach (1pt.). Based on this scoring, the quality of each study was classified as good (≥ 8/10 points [incl. good design and diagnosis]); fair (≥ 6/10 points [incl. ≥ 1 pt. on intervention]); or poor (≤ 5/10 points). Of the 63 studies included in the 2014 AHRQ Report, 18, 37, and 8 studies were classified as good, fair, or poor, respectively.

Strength of Evidence Assessment

The Strength of Evidence (SOE) was judged separately for important, global questions (e.g., Are ABA-based Early Intensive Behavioral & Developmental Interventions effective for increasing IQ/cognitive abilities? How confident are we that these effects will be stable considering future research?). For each question, SOE was determined based on a qualitative synthesis of the entire body of research, considering the following domains: (1) Study limitations (Overall quality of the included studies); (2) Consistency (Do studies find the same direction or similar magnitude of effect?) (3) Directness (Could the effect be attributed to other factors beside the evaluated intervention?); (4) Precision: (certainty about the effect estimate); and (5) Reporting bias (concerns about selective publishing). For each research question, SOE grades were assigned to indicate the following levels:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.
- Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion.

ABA-based Early Intensive Behavioral & Developmental Approaches

Definition/Explication: This broad category of intervention approaches shares the following elements, as described in the AHRQ Report (Weitlauf et al, 2014):

- Intervention strategies are derived from applied behavior analysis (ABA). The goal of ABA is to teach new skills, promote generalization of these skills, and reduce challenging behaviors with systematic reinforcement.
- Use of high-intensity (i.e., many hours per week, one-on-one) instruction.
- Approaches differ substantially in terms of their structure (i.e., intensity, duration, parent component), approach (i.e., discrete trial, developmental), & setting (i.e., home, clinic, classroom).
- Included are manualized approaches and more eclectically defined and delivered approaches. Examples of manualized approaches include: (1) UCLA/Lovaas: Relies heavily on one-on-one therapy sessions during which a trained therapist uses discrete trial teaching with a child to practice target skills; (2) Learning Experiences and Alternative Program (LEAP): Incorporates a range of strategies, including peer mediated social skills training, incidental teaching, pivotal response training, Picture Exchange

Communication System (PECS), and positive behavior support; and (3) Early Start Denver Model (ESDM): Blends ABA principles with developmental and relationship-based approaches for young children.

Key Findings of the 2014 AHRQ Report ABA-based Early Intensive Behavioral & Developmental Approaches

In summarizing the findings of their review, Weitlauf et al. (2014) drew the following conclusions on strength of evidence for outcomes of early intensive behavioral and developmental interventions based on principles of ABA (Executive Summary, pp. 12-13).

- IQ/cognitive outcomes (Moderate for positive effect): both treatment and comparison groups showed improvement in some areas of cognition. Children receiving early intensive behavioral interventions showed more improvement than those receiving other types of services. On long-term follow-up, not all improvements were maintained.
- Adaptive behavior outcomes (Low for positive effect): both treatment and control groups showed improvement in adaptive skills, with children receiving early intervention behavioral interventions showing more improvement. On long-term follow-up, not all group differences were maintained.
- Symptom severity outcomes (Low for positive effect): two studies of good quality that showed positive effects; however, a number of lower quality studies did not find impact on symptom severity. Additional studies are needed to confirm positive effects of intervention on symptom severity.
- Language/communication outcomes (Moderate for positive effect): a positive effect on language was found overall. Most studies reviewed showed a positive treatment effect; however, there were differences in the specific domain of improvement (for example, receptive vs. expressive language) across studies. On long-term follow-up, some initial between-group differences were no longer evidenced.
- Social skills/social behavior outcomes (Low for positive effect): many studies reviewed found more improvement in treatment groups than control groups in this outcome area; however, no treatment effect was found for a significant minority of studies. Positive effects were observed but not consistently.

New Evidence Contributed by Current Review

Table E-8 Summary of new evidence reviewed from studies completed 2012-2015

Author	Context	Design	Type of control	N	Age	Intervention	Intensity
D'Elia et al., 2014	Classroom w/ Parent Education	Quasi-Experiment	Active Control	15	49.2 (14.4)	TEACCH	~ 184 staff/parent training sessions over 24 months
Dawson et al., 2010; Dawson et al., 2012; Estes et al., 2015;	Individual w/parent	Single-Site Randomized Controlled Trial	TaU*	24	23.9 (4.0)	Early Start Denver Model (ESDM)	~ 20 h/wk for 24 months
Howard, Stanislaw, Green,	Individual w/parent	Quasi-Experiment	Active Control	29	30.9 (5.2)	Intense Behavior Analytic	~ 25-40 h/wk for 37 months

Table E-8 Summary of new evidence reviewed from studies completed 2012-2015							
Sparkman, & Cohen, 2014						Treatment (ABA)	
Mandell et al., 2013	Classroom	Quasi-Experiment	TEACCH	60	74.4 (4.8)	Strategies for Teaching based on Autism Research (STAR)/ ABA	~ 100 hours of staff training over 9 months
Nahmias, Kase, & Mandell, 2014	Classroom	Quasi-Experiment	Mixed Disability/ Autism-only Preschool Setting	25	40.7 (7.9)	Inclusive Preschool Setting	n/a
Paul, Campbell, Gilbert, & Tsiouri, 2013	Individual w/parent	Quasi-Experiment	Milieu Communication Training	10	51.6 (14.4)	Rapid Motor Imitation Antecedent/ Discrete Trial Training	40 sessions over 3 months
Stock, Mirenda, & Smith, 2013	Individual w/parent	Quasi-Experiment	Pivotal Response Treatment (PRT)/ ABA	12	46.0 (8.1)	Verbal Behavior/ ABA	~ 20 h/wk for 12 months
Van der Paelt, Warreyn, & Roeyers, 2014	Individual	Quasi-Experiment	Active Control, TaU	20	44.5 (16.3)	Applied Behavior Analysis (ABA)	~ 4 h/wk for 6 months
Vivanti et al., 2014	Classroom w/ Parent Education	Quasi-Experiment	Active Control	27	40.3 (9.6)	ESDM group program	~ 20 h/wk for 12 months
**Treatment as usual*							

Summary and conclusions based on new evidence

- Overall, the conclusions of the 2014 AHRQ Report (including SOE Grades) are supported by recent evidence.
- Two recent studies that followed children two to three years after Early Intensive Intervention show some maintenance of IQ/language/adaptive skills effects (Howard et al., 2005; 2014; Dawson et al. 2010; 2012; Estes et al., 2015).
- Four recent studies tested interventions for young children with ASD that were implemented in a classroom setting (Mandell et al., 2013; Nahmias, Kase, & Mandell, 2014; Vivanti et al., 2014; D'Elia et al., 2014). Rigorous research testing the efficacy of professional development programs for teachers, that aim to increase access to inclusive, classroom-based learning environments for toddlers and preschoolers with ASD, provide an important new development in intervention research. Early Child Care and Head Start programs provide an important aspect of children's early learning environment, and may provide an important context for naturalistic, developmental interventions for toddlers and preschoolers with ASD.
- Three recent studies that compared intensive early intervention programs based on traditional ABA vs. developmental approaches failed to identify differential effects (Stock et al., 2013; Paul et al., 2013; Van der Paelt et al., 2014).

- One recent effectiveness study that compared intense ABA-based and Structured Teaching (TEACCH) strategies implemented in a classroom setting failed to identify significant treatment effects on IQ (Mandell et al., 2013).
- One recent quasi-experimental study that compared inclusive vs. self-contained preschool settings reported treatment effects on IQ favoring children attending inclusive settings (Nahmias et al., 2014).

Behavioral & Developmental Early Intervention – Parent Training

Definition/Explication: This broad category of intervention approaches shares the following elements, as described in the AHRQ Report (Weitlauf et al., 2014):

- Parent training approaches that use principles of behavioral learning to focus on key pivotal behaviors rather than global improvements.
- May focus on social-communication skills or specific behaviors, such as initiating activities.
- Individual approaches vary in terms of approach, scope, and intensity.
- Specific approaches that were considered in the 2014 AHRQ Review include (1) Pivotal Response Training (PRT), (2) Hanen's "More Than Words" (HMTW), (3) Parent delivery – Early Start Denver Model (P-ESDM), (4) Milton & Ethel Harris Research Initiative Treatment (MEHRIT)/ Parent administered DIR/Floortime, and (5) Preschool Autism Communication Trial (PACT).

Key Findings of the 2014 AHRQ Report – Behavioral & Developmental Early Intervention – Parent Training (Executive Summary, p. 14)

In summarizing the findings of their review, Weitlauf et al. (2014) drew the following conclusions on strength of evidence for outcomes of early intensive behavioral and developmental interventions – parent training approaches (Executive Summary, p. 14):

- IQ/cognitive outcomes (Low for positive effect): relative to community-based interventions, most of the studies of parent-implemented ABA found no improvements in IQ. Some studies reported worse outcomes for parent-implemented ABA in relative to center-based treatment.
- Symptom severity outcomes (Low for positive effect): treatment groups were found to have improvements in severity of ASD symptoms relative to control groups in many studies.
- Language/communication outcomes (Low for positive effect): although parent training was found to be associated with language improvements, interventions and comparators differed across studies. Outcome measures used across studies were also different. Additional studies are needed.

New Evidence Contributed by Current Review

Table E-9 Summary of new evidence reviewed from studies completed 2012-2015

Author	Context	Design	Type of control	N	Age	Intervention	Intensity
Carter et al., 2011; Lieberman-Betz et al., 2014	Parent	Multi-Site Randomized	TaU*	32	21.1 (2.7)	HMTW	~11 sessions over 5 months

Table E-9 Summary of new evidence reviewed from studies completed 2012-2015							
Author	Context	Design	Type of control	N	Age	Intervention	Intensity
		Controlled Trial					
Casenhiser, Binns, McGill, Morderer, & Shanker, 2015; Casenhiser, Shanker, & Stieben, 2013	Parent	Single-Site Randomized Controlled Trial	TaU	25	42.5 (8.8)	MEHRIT/ DIR	~52 sessions over 12 months
Green et al., 2010; Pickles et al., 2015	Parent	Multi-Site Randomized Controlled Trial	TaU	77	45 (26-60)	PACT	~19 sessions over 12 months
Hardan et al., 2015	Parent	Single-Site Randomized Controlled Trial	TaU	25	49.2 (14.4)	PRT	~12 sessions over 3 months
Solomon, Van Egeren, Mahoney, Huber, & Zimmerman, 2014	Parent	Multi-Site Randomized Controlled Trial	TaU	64	49.9 (10.4)	Play Project/ DIR	~12 sessions over 12 months
Stadnick, Stahmer, & Brookman-Frazee, 2015	Parent	Quasi-Experiment	TaU	16	46.8 (25.9)	Project ImPACT	~12 sessions over 3 months
Tonge, Brereton, Kiomall, Mackinnon, & Rinehart, 2014	Parent	Single-Site Randomized Controlled Trial	Active Control	35	46 (8)	Parent Education & Behavior Management	~ 20 sessions over 5 months
Welterlin, Turner-Brown, Harris, Mesibov, & Delmolino, 2012	Parent	Single-Site Randomized Controlled Trial	TaU	10	30.2 (3.6)	Home TEACCHing Program/ TEACCH	~12 sessions over 3 months
Wetherby et al., 2014	Parent	Multi-Site Randomized Controlled Trial	Active Control	42	19.6 (1.9)	Early Social Interaction/ SCERTS	~ 94 sessions over 8 months
**Treatment as usual*							

Summary and conclusions based on current evidence

- Overall, results from our review of literature published between 2013 and 2015 revealed growth in rigorous intervention research testing the efficacy of parent training/coaching interventions (nine studies were identified with newly published data).
- Five recent studies show significant treatment effects on communication/language (Tonge et al., 2014; Wetherby et al., 2014; Green et al., 2010; Pickles et al., 2015; Hardan et al., 2015; Stadnick et al., 2015). Given this recent evidence, it was concluded to update the SOE grade with regards to language/communication outcomes to 'Medium for positive effect'.
- Four recent studies show significant treatment effects on adaptive behaviors (Tonge et

al., 2014; Wetherby et al., 2014; Hardan et al., 2015; Stadnick et al., 2015). Given this recent evidence, it was concluded to address a new intervention outcome (adaptive behaviors), which was graded as 'Low for positive effect'.
- Two recent studies demonstrate improvements in ASD symptoms (Solomon et al., 2014; Green et al., 2010; Pickles et al., 2015). SOE grade of 'Low for positive effect' remained unchanged.
- Seven recent studies show that parent training/coaching interventions increase various aspects of the families' capacity to meet the needs of young children with ASD (e.g., increases in the quality of parent-child interaction; Casenhiser et al., 2013; 2015; Solomon et al., 2014; Tonge et al., 2014; Wetherby et al., 2014; Green et al., 2010; Pickles et al., 2015; Hardan et al., 2015; Stadnick et al., 2015). Given this recent evidence, it was concluded to address a new intervention outcome (family capacity building), which was graded as 'Medium for positive effect'.
- Comparisons between different parent training/coaching interventions suggest that generalized intervention outcomes on language/communication, adaptive behavior, and symptom severity are more likely if interventions are more intense, longer-term, include guided practice with feedback, and are embedded in natural family routines.

Play-/Interaction-Focused Intervention Approaches

Definition/Explication: This broad category of intervention approaches shares the following elements, as described in the AHRQ Report (Weitlauf et al., 2014):

- Use interactions between children and parents or clinician to affect outcomes such as imitation or joint attention skills or the ability of the child to engage in symbolic play.
- Specific approaches that were considered in the 2014 AHRQ Review include (1) Joint Attention Symbolic Play Emotion Regulation (JASPER), (2) Focused Playtime Intervention (FPI), (3) Reciprocal Imitation Training, (4) Joint Attention Mediated Learning, and (5) Parent-Child Interaction Therapy

Key Findings of the 2014 AHRQ Report – Play/Interaction-Focused Intervention Approaches

In summarizing the findings of their review, Weitlauf et al. (2014) drew the following conclusions on strength of evidence for outcomes of early intensive behavioral and developmental interventions – parent training approaches (Executive Summary, p. 15).

- Joint attention outcomes (Moderate for positive effect): joint attention skills were found to increase for children in treatment groups. However, children in most studies were also receiving other types of early intervention. Duration of treatment effects is unclear.
- Play skill outcomes (Low for positive effect): "Play skills increased in treatment arms but duration of effects is unclear. Imitation skills improved in treatment arms in 4 small short-term studies and in the treatment and control arms in 1 study."
- Language/communication outcomes (Low for positive effect): "Expressive, but not receptive, language skills generally increased in the treatment arms in 2 studies; prompted, but not spontaneous, communication improved in 1 study."
- Social skill outcomes (Low for positive effect): "Joint engagement or positive affect improved in treatment arms in 3 studies."

New Evidence Contributed by Current Review

Table E-10 Summary of new evidence reviewed from studies completed 2012-2015							
Author	**Context**	**Design**	**Type of control**	**N**	**Age**	**Intervention**	**Intensity**
Carr et al., 2015; Kasari, Lawton, et al., 2014	Parent	Multi-Site Randomized Controlled Trial	Active Control	60	41.9 (10.0)	Joint Attention Structured Play Emotion Regulation (JASPER)	~24 sessions over 3 months
Chiang, Chu, & Lee, 2015	Parent	Quasi-Experiment	TaU*	18	35.9 (8.6)	Joint Attention Structured Play Emotion Regulation (JASPER)	~20 sessions over 8 weeks
Ginn, Clionsky, Eyberg, Warner-Metzger, & Abner, 2015	Parent	Single-Site Randomized Controlled Trial	TaU	15	51.6 (14.4)	CDIT/ PCIT	~8 sessions over 2.5 months
Gulsrud et al., 2014; Kasari et al., 2006; Kasari et al., 2012; Kasari et al, 2008	Individual	Single-Site Randomized Controlled Trial	Active Control, TaU	20 [JA group], 21 [SP group]	43 (7) [JA group], 43 (7) [SP group]	Joint Attention Structured Play Emotion Regulation (JASPER)	~ 30 sessions over 1.5 months
Iwanaga et al., 2014	Individual	Quasi-Experiment	Active Control	8	(31-74)	Sensory Integration Therapy	~ 43 sessions over 10 months
Kaale et a., 2014; Kaale, Smith, & Sponheim, 2012	Individual	Single-Site Randomized Controlled Trial	TaU	34	47.6 (8.3)	Joint Attention Structured Play Emotion Regulation (JASPER)	~ 80 sessions over 2 months
Kamps et al., 2016	Classroom	Multi-Site Randomized Controlled Trial	TaU	56	69.6 (62 - 82)	Peer network intervention	~ 156 sessions over 18 months
Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015	Parent	Single-Site Randomized Controlled Trial	Active Control	43	30.7 (3.5)	Joint Attention Structured Play Emotion Regulation (JASPER)	~20 sessions over 2.5 months
Kasari, Siller, et al., 2014	Parent	Multi-Site Randomized Controlled Trial	Active Control	32	22.2 (4.2)	Focused Playtime Intervention (FPI)	~12 sessions over 3 months

Table E-10 Summary of new evidence reviewed from studies completed 2012-2015							
Author	**Context**	**Design**	**Type of control**	**N**	**Age**	**Intervention**	**Intensity**
Lerna, Esposito, Conson, Russo, & Massagli, 2012; Lerna, Esposito, Conson, & Massagli, 2014	Individual	Quasi-Experiment	Active Control	9	38.8 (7.4)	Picture Exchange Communi-cation System (PECS)	~ 78 sessions over 6 months
McDuffie, Lieberman, & Yoder, 2012; Yoder & Stone, 2006a, 2006b	Individual w/parent	Single-Site Randomized Controlled Trial	PECS	16	32.4 (6.0)	Responsive Education & Prelinguistic Milieu Teaching	~ 88 sessions over 6 months
Porges et al., 2014	Individual	Single-Site Randomized Controlled Trial (2 separate RCTs)	Active Control	36 [RCT1], 50 [RCT2]	55 (11) [RCT1], 53 (16) [RCT2]	Listening Project Protocol	~ 5 sessions over 0.25 months
Poslawsky et al., 2015	Parent	Single-Site Randomized Controlled Trial	TaU	40	42.2 (9.0)	Video Interaction to promote Pos. Parenting (VIPP)	~ 5 sessions over 3 months
Sanefuji & Ohgami, 2013	Parent	Single-Site Randomized Controlled Trial	Active Control	8	54 (34 - 71)	Contingent Imitation	~ 1 session
Siller, Hutman, & Sigman, 2013; Siller, Swanson, Gerber, Hutman, & Sigman, 2014	Parent	Single-Site Randomized Controlled Trial	Active Control	36	58.3 (12.7)	Focused Playtime Intervention (FPI)	~12 sessions over 3 months
Silva & Schalock, 2013	Parent	Quasi-Experiment	TaU	97	46.8 (13.2)	Qugong Sensory Treatment	~ 21 sessions over 5 months
Silva et al., 2015	Parent w/ individual	Multi-Site Randomized Controlled Trial	TaU	55	(24 - 60)	Qugong Sensory Treatment	~ 21 sessions over 5 months
Thompson, McFerran, & Gold, 2014	Parent	Single-Site Randomized Controlled Trial	TaU	12	44 (6)	Family Centered Music	~16 sessions over 4 months

Table E-10 Summary of new evidence reviewed from studies completed 2012-2015							
Author	**Context**	**Design**	**Type of control**	**N**	**Age**	**Intervention**	**Intensity**
						Therapy (FCMT)	
Woo, Donnelly, Steinberg-Epstein, & Leon, 2015	Parent	Single-Site Randomized Controlled Trial	TaU	28	57.6 (13.2)	Sensorimotor exercises	~ 1 session/ 13 contacts over 6 months
**Treatment as usual*							

Summary and conclusions based on current review

- There was a total of 19 studies published between 2013 and 2015 testing the efficacy of Play-/Interaction-Focused Intervention Approaches.
- The majority (11) of these studies tested interventions delivered in the context of parent-child interaction, while 4 studies tested interventions delivered during interactions between the child and a clinician (3 studies used a combined approach; 1 study focused on peer interactions).
- Four recent studies show significant treatment effects on joint attention behaviors (Carr et al., 2015; Kasari, Lawton, et al., 2014; Poslawsky et al., 2015; Kaale et a., 2014; Kaale, Smith, & Sponheim, 2012; Lerna, Esposito, Conson, Russo, & Massagli, 2012; Lerna, Esposito, Conson, & Massagli, 2014). SOE grade of 'Medium for positive effect' remained unchanged.
- Two recent studies show significant treatment effects on play behaviors (Ginn, Clionsky, Eyberg, Warner-Metzger, & Abner, 2015; Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015). SOE grade of 'Low for positive effect' remained unchanged.
- Seven recent studies show significant treatment effects on social behaviors, including joint engagement, attachment-related behaviors and social/emotional functioning (Carr et al., 2015; Kasari, Lawton, et al., 2014; Siller, Hutman, & Sigman, 2013; Siller, Swanson, Gerber, Hutman, & Sigman, 2014; Thompson, McFerran, & Gold, 2014; Kaale et a., 2014; Kaale, Smith, & Sponheim, 2012; Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015; Chiang, Chu, & Lee, 2015; Kamps et al., 2016). SOE grade of 'Low for positive effect' remained unchanged.
- Five recent studies show that play/Interaction-focused intervention approaches increase various aspects of the families' capacity to meet the needs of young children with ASD (e.g., increases in the quality of parent-child interaction; Ginn, Clionsky, Eyberg, Warner-Metzger, & Abner, 2015; Kasari, Siller, et al., 2014; Siller, Hutman, & Sigman, 2013; Siller, Swanson, Gerber, Hutman, & Sigman, 2014; Poslawsky et al., 2015; McDuffie, Lieberman, & Yoder, 2012; Yoder & Stone, 2006a, 2006b). Given this recent evidence, it was concluded to address a new intervention outcome (family capacity building), which was graded as 'Medium for positive effect'.
- Four recent studies show significant treatment effects on sensory-regulation symptoms (Silva et al., 2015; Woo, Donnelly, Steinberg-Epstein, & Leon, 2015; Porges et al., 2014; Iwanaga et al., 2014; Silva & Schalock, 2013). Given this recent evidence, it was concluded to address a new intervention outcome (Sensory-regulation outcomes), which was graded as 'Low for positive effect'.

Other Intervention Approaches

Interventions for High-Risk Infants

Four recently published studies testing parent coaching interventions for parents of infants (< 12 months) at high risk for ASD were reviewed (Rogers et al., 2014; Green et al., 2015; Green et al., 2013; Baranek et al., 2015). The evidence on the efficacy of such interventions does not permit a conclusion at this point in time (SOE grade: Insufficient).

Table E-11. Summary of new evidence reviewed from studies completed 2012-2015

Author	Context	Design	Type of control	N	Age	Intervention	Intensity
Baranek et al., 2015	Parent	Randomized Controlled Trial	TaU*	11	15.2 (1.2)	Adapted Responsive Teaching	~24 sessions over 4.5 months
Green et al., 2014	Parent	Quasi-Experiment	TaU	7	8.4 (.8)	Video Interaction to promote Positive Parenting (VIPP)	~12 sessions over 5 months
Green et al., 2015	Parent	Multi-Site Randomized Controlled Trial	TaU	28	8.8 (.6)	Video Interaction to promote Positive Parenting (VIPP)	~ 9 sessions over 5 months
Rogers et al., 2014	Parent	Quasi-Experiment	TaU	7	(7-15)	Infant Start/ ESDM	~ 12 sessions over 3 months

**Treatment as usual*

Interventions for Challenging Behaviors and Sleep

Three recently published studies testing parent training interventions targeting challenging behaviors and sleep problems were reviewed (Grahame et al., 2015; Bearss et al., 2015; Johnson et al., 2013). The number of controlled group studies published to date is small. Given this limitation, the available evidence about the efficacy of such interventions does not permit a conclusion at this point in time (SOE grade: Insufficient).

Table-12. Summary of new evidence reviewed from studies completed 2012-2015

Author	Context	Design	Type of control	N	Age	Intervention	Intensity
Bearss et al., 2015	Parent	Multi-Site Randomized Controlled Trial	Active Control	89	57.6 (14.4)	Parent Training/ ABA	~ 19 sessions over 4 months
Grahame et al., 2015	Parent	Single-Site Randomized Controlled Trial	TaU*	25	60.4 (14.0)	Managing Repetitive Behaviors/ ABA	~ 10 sessions over 2.5 months
Johnson et al., 2013	Parent	Single-Site Randomized	Active Control	15	42 (12)	Behavior Parent	~ 5 sessions over 2 months

Table-12. Summary of new evidence reviewed from studies completed 2012-2015							
Author	Context	Design	Type of control	N	Age	Intervention	Intensity
		Controlled Trial				Training/ ABA	
**Treatment as usual*							

Interventions to Increase Parent knowledge & well-being

Three recently published studies testing interventions to increase parent knowledge about autism and improve parent well-being were reviewed (Zhang, Yan, Du, & Liu, 2014; Feinberg et al., 2014; Suzuki et al., 2014). In addition, four parent training/coaching approaches discussed above show intervention effects on parent self-efficacy and stress (Poslawsky et al., 2015; Silva et al., 2015; Kasari, Gulsrud, Paparella, Hellemann, & Berry, 2015; Silva et al., 2015). Available evidence about the efficacy of such interventions does not permit a conclusion at this point in time (SOE grade: Insufficient).

Table E-14 Summary of new evidence reviewed from studies completed 2012-2015							
Author	Context	Design	Type of control	N	Age	Intervention	Intensity
Feinberg et al., 2014	Parent	Single-Site Randomized Controlled Trial	TaU*	59	34 (10)	Problem Solving Education/ CBT	~ 6 sessions over 3 months
Suzuki et al., 2014	Parent	Single-Site Randomized Controlled Trial	TaU	36	52.8 (9.6)	Psychoeducation Group	~ 4 sessions over 2 months
Zhang, Yan, Du, & Liu, 2014	Parent	Quasi-Experiment	TaU	18	54 (25.2)	Solution-Focused Brief Therapy/ CBT	~ 6 sessions over 1.5 months
**Treatment as usual*							

E.4 Conclusions of the Review

Overall Summary

Sixty-one peer-reviewed journal articles were identified that met minimum quality and applicability standards for studies providing adequate evidence about the efficacy of the evaluated interventions. The identified research articles reported on the results of 47 unique research studies. Results show that 31 studies (66%) reported on a Randomized Controlled Trial, while 16 studies used a Quasi-Experimental design. Results also showed that 31 studies (66%) evaluated parent-mediated interventions, while 11 (23%) and 5 (11%) studies were implemented individually or in a classroom context, respectively.

In the category of ABA-based Early Intensive Behavioral and Developmental Interventions, two studies that followed children two to three years after early intensive intervention show some maintenance of IQ/language effects, supporting the AHRQ (2014) strength of evidence grades (*Medium for positive effect on IQ/cognitive abilities; Medium for positive effect on language/communication)*.

In the category of Behavioral & Developmental Early Intervention-Parent Training, five new studies show significant treatment effects on communication/language, constituting a strength of evidence rating of *Medium for positive effect*. Four new studies show significant treatment effects on adaptive behaviors, constituting a strength of evidence rating *Low for positive effect*. Two new studies demonstrate improvements in ASD symptoms, constituting a strength of evidence rating *Low for positive effect*. Significant treatment effects were found for parent responsiveness/stress/attachment, constituting a strength of evidence rating of *Medium for positive effect* on family capacity-building.

In the category of Play-/Interaction-Based Interventions, three new studies show significant treatment effects on joint attention, concluding that the strength of evidence grade stands. Three new studies show significant treatment effects on social behaviors, again concluding that the strength of evidence grade stands. Six new studies show significant treatment effects on parenting outcomes, constituting a strength of evidence rating of *Medium for positive effect* on family capacity-building. Four new studies show significant treatment effects on sensory-regulation symptoms, constituting a strength of evidence rating of *Low for positive effect* on sensory-regulation symptoms.

In terms of "Other Intervention Approaches", such as interventions for 'high risk' infants, Interventions for Challenging Behaviors, Sleep Interventions, and Interventions targeting parent knowledge and well-being the results were mixed, leading to a general conclusion of insufficient. The strength of evidence supporting efficacy on child outcomes is insufficient.

Strength of Evidence

A summary of the broad questions evaluated, the SOE grades included in the 2014 AHRQ Report, as well as the updates based on the current review of articles published after the deadline for inclusion in the AHRQ report (2012-2015) are summarized in Table C-39. Consistent with the 2014 AHRQ Report, this review considered evidence with regards to three broad categories of intervention approaches: (1) ABA-based Early Intensive Behavioral & Developmental Approaches, (2) Behavioral & Developmental Early Intervention-Parent Training, and (3) Play-/Interaction-Focused Intervention Approaches.

Table E-15. Summary of broad questions evaluated, SOE grades included in the 2014 AHRQ Report, and updates based on articles in current review

Outcome	**Strength of Evidence Grade**	
	2014 AHRQ Report	**2015 Review**
ABA-based Early Intensive Behavioral and Developmental Interventions		
IQ/cognitive abilities	Medium for positive effect	Medium for positive effect
Adaptive behavior	Low for positive effect	Low for positive effect
Symptom severity	Low for positive effect	Low for positive effect
Language/communication	Medium for positive effect	Medium for positive effect
Social skills/social behavior	Low for positive effect	Low for positive effect
Behavioral & Developmental Early Intervention-Parent Training		

Table E-15. Summary of broad questions evaluated, SOE grades included in the 2014 AHRQ Report, and updates based on articles in current review		
Outcome	**Strength of Evidence Grade**	
	2014 AHRQ Report	**2015 Review**
IQ/cognitive abilities	Low for no effect	Low for no effect
Symptom severity	Low for positive effect	Low for positive effect
Language/communication	Low for positive effect	Medium for positive effect*
Adaptive behaviors	-	Low for positive effect*
Family Capacity Building	-	Medium for positive effect*
Play-/Interaction-Based Interventions		
Joint Attention	Medium for positive effect	Medium for positive effect
Play Skills	Low for positive effect	Low for positive effect
Language/communication	Low for positive effect	Low for positive effect
Social Skills	Low for positive effect	Low for positive effect
Sensory-regulation	-	Low for positive effect*
Family Capacity Building	-	Medium for positive effect*
*The Strength of Evidence Grade was changed in light of the current literature review.		

Report of Research for Medical Evaluation, Associated Conditions, and Interventions for Children with Autism Spectrum Disorders

Summary of Research Literature on Medical Evaluation, Associated Conditions, and Interventions for Children with Autism Spectrum Disorders: 1999-2014

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F. Medical Evaluation, Associated Conditions, and Interventions for Children with Autism Spectrum Disorders

F.1 Literature search

Due to the biomedical nature of this topic area, this review depended primarily on Medline /Pubmed to search for peer reviewed literature published on the included topic areas between January,1999 and August 2014. The initial search was completed between March and June 2014 with updated review through August 2014. Articles were included if they documented autism, Asperger Syndrome, autism spectrum disorders or pervasive developmental disorder in the population examined. The topic areas were explored using synonyms and related topic names as well as searching through other developmental disorders other than ASD. The computerized search was supplemented by collection of articles referenced in reviews and research articles. Reference lists for all articles reviewed were cross referenced with the automated search through PubMed.

F.2 Selecting articles for review

A total of 6380 unique articles published in English were identified and considered for inclusion in this review. Abstracts obtained from computerized bibliography searches were screened using established criteria. All topic areas included in the 1999 NYSDOH ASD Guideline review were included in addition to topic areas that have become important in the past 15 years. The article needed to include children ages 0- 8 years of age with a diagnosis of autism, Asperger Syndrome, autism spectrum disorder and/or pervasive developmental disorder not otherwise specified; it needed to present new data collected for the study (not a review article, description of a hypothesis, or editorial) or provide a new analysis of a dataset. If an intervention (as opposed to a study of comorbid conditions) was reported, the trial needed to describe how they made the diagnosis of the ASD and describe an evidence based approach to methodology and interpretation of data. Case reports or single subject cases were not included in the biomedical section. Any article that failed to meet these criteria was not included.

From the full list of 6,380 unique articles, the screening process yielded 667 articles for full-text review. A total of 229 articles met criteria for providing evidence about the prevalence, efficacy of intervention, or contribution of medically related conditions that impact therapy or their treatments for young children with ASD. Some studies resulted in multiple publications on different aspects of the data. Detailed information on each of the selected articles is presented in the evidence tables included in the appendices. Diet therapies, dietary supplements used as therapy and biologic therapies were combined into one category for the summary data.

F.3 Considerations for the review of evidence

The criteria developed by the 1999 NYSDOH ASD Guideline panel were used for full text review. These criteria specified acceptable quality and standards for the evidence used to evaluate medical evaluations, tests and interventions as well as association with comorbid conditions that may impact care. If an article failed to meet one or more of these evaluation criteria, it was dropped from further consideration. Articles needed to be published in English, include children 0-8 years of age with an autism spectrum disorder, present original data on one of the topic areas of this review, provide adequate description of the intervention or test, treatment interventions needed to have documented whether they used a control group or

crossover design, and if description of prevalence included comparison to the population from which the participants were selected.

F.4 Results of research review

The purpose of this review was to identify and assess the empirical literature evaluating the medical evaluation – including laboratory evaluation for etiology - for young children with ASD, the comorbid medical conditions that are present in young children with ASD that may impact well-being, family function, and participation in intervention and should be considered in the medical evaluation once the diagnosis of ASD is made; and biomedical interventions of both standard and nonstandard types. To that end, the report of the review is organized according to the evidence for associated conditions, dietary and novel therapies, medications, and etiological work up.

Research design and focus

The summary of study designs is displayed in the following table. The designs varied across topic areas since demonstration of association of medical comorbidities to alert providers of the potential impact on therapy are based in comparison of prevalence to an appropriate control group. Intervention studies used a randomized controlled group design, open label design, or retrospective data analysis. The double blind, randomized, placebo controlled trials provide the most compelling data for review of practice guidelines, however the other designs are often included in critical reviews that shape clinical practice to supplement existing randomized, controlled trials. Open label studies are often part of conventional drug trials to assess long term effects after an initial randomized double blind trial. Open label trials and retrospective analyses are also reported as preliminary documentation of potential effect to justify additional study. Many outcomes were initially broad, but with additional study became more targeted (such as irritability and repetitive behaviors with atypical antipsychotic agents like risperidone.

Table F-1 Summary of Study Designs

Category	Associated Conditions	Dietary and Novel Therapies	Medications	Etiologic Work Up
DBRCT	-	11	31	-
Single Blind RCT	-	3	19	-
Random parallel assignment	-	-	1	-
Retrospective	18	3	9	10
Population samples	14	-	-	13
Registry samples	6	3	-	11
Prospective Recruitment	8	-	-	27
Case Series	1	-	-	8
Case Control	3	-	-	6

Number of research articles by publication year

The research articles included in this review were tabulated by publication year. The studies related to associated conditions increased over the first 9 years of the review interval as the concept of co-morbid medical conditions was popularized by the Autism Treatment Network and recognition of the potential for medical conditions to impact behavioral symptoms. More reviews were published in more recent years. Articles related to etiologic work up increased as advances in genetics made routine and cost effective chromosomal microarray possible. Studies focusing on the success of atypical neuroleptics followed on the heels of the publication of the initial Research Units in Pediatric Pharmacology trial in 2002 (McCracken, 2002) documenting the efficacy of risperidone on irritability in children with ASD. Especially related to diet and dietary therapy, there have been many review and summary articles based on a small number of evidence based publications.

Table F-2. Number of Studies Reviewed by Year Published

Year	Associated Conditions	Diet/Dietary Therapy	Medications	Work up	Total per year
1999	-	-	-	-	-
2000	-	-	1	1	2
2001	2	-	4	3	9
2002	1	3	6	-	10
2003	4	-	1	5	10
2004	1	2	6	1	10
2005	4	1	9	8	22
2006	6	4	7	8	25
2007	3	2	-	6	11
2008	12	2	6	6	26
2009	7	3	3	8	21
2010	6	2	4	7	19
2011	3	5	3	8	19
2012	5	5	5	8	23
2013	7	-	5	7	19
2014	1	2	-	-	3*
**Primarily reflects first months of the year*					

Age of child participants

Few studies were limited to children less than 8 years of age. Genetic and metabolic studies report on data that does not change with age (genetic findings) so the age range in these papers need not be limited to less than 8. Indeed, many large genetic registries did not report the age of the probands. Medication trials often included children 4 and 5 years of age with an age range extending to either 11/12 or 17 depending on whether the investigators wanted to include post pubertal children. Medications were increasingly prescribed to children with ASD under the age of 8 in the interval since the last guideline publication (Coury, 2012).

F-3. Age of Subjects by Focus Area				
Ages of Subjects	Associated Conditions	Diet/Dietary Therapy	Medications	Work Up
All less than 8 yrs	18	7	6	16
Some less than 8, some older	44	24	53	41
Unknown or age not relevant	-	-	1	19

Country where the research was conducted

The following table reports on the countries in which studies were performed in each category. Few studies performed outside of the US included race/ethnicity data. Several in China and Japan note that the participants were Chinese and Japanese respectively, and one in Jamaica noted AfroCarribbean descent of all participants. There is great international interest in autism as demonstrated by the research sites. Some countries with disease registries (e.g. Denmark) or national health systems (eg. UK, Finland) make possible access to medical data that are conducive to the type of clinical research that establishes medical comorbidities for ASD.

Table F-3 Focus Area by Country and Number of Studies		
Focus Area	Country	Number of Studies
Associated Medical conditions		
Conditions with increased risk	Brazil	1
	Canada	1
	China	1
	Finland	2
	Italy	1
	Netherlands	1
	Sweden	2
	Taiwan	1
	US	6
Dental	US	1
GI	Australia	1
	Brazil	1
	Canada	1
	Netherlands	1
	Sweden	1
	UK	4
	US	7
Immunologic	US	4
Seizures	Iceland	2
	Italy	4
	Spain	1

Table F-3 Focus Area by Country and Number of Studies		
Focus Area	Country	Number of Studies
	Sweden	1
	UK	1
	US	3
	Multiple	1
Sleep	Finland	1
	Sweden	1
	US	7
Diet and Dietary Therapies and Novel Therapies		
Dietary therapy	Denmark	1
	Hong Kong	1
	Norway	1
	US	3
Obesity	US	3
B6	France	1
B12 and antioxidants	US	3
Enzymes	Australia	1
Iron	Australia	1
	Canada	1
	Turkey	1
	US	1
L carnosine	US	1
Melatonin	Italy	1
	UK	1
	US	3
Multivitamin	US	1
Omega 3 Fatty acids	Austria	1
	Egypt	1
	Israel	1
	US	1
HBOT	US	2
Medications		
Alpha 1 blocker	US	4
Amantidine	US	1
Anti-anxiety	US	1
Antibiotic	US	1
Anticonvulsant	Iran	1
	Italy	1
	US	3
Atypical Neuroleptic	India	1
	Iran	4

Table F-3 Focus Area by Country and Number of Studies		
Focus Area	Country	Number of Studies
	Turkey US	2 16
Donezepil	US	2
Immunoglobins	US	1
Medication/Parent management	US	1
Memantine	US	2
N-Acetyl Cystine	US	1
Secretin	Canada US	1 2
SNRI (atomoxetine)	Netherlands Norway US	2 1 1
SSRI	US	5
Stimulants	US	3
Tricyclic Antidepressants	Turkey US	1 2
Work Up		
EEG	Canada	1
Exposure history	Denmark Hong Kong Jamaica Japan Saudi Arabia UK US	1 2 1 1 1 1 9
Genetics	Australia China France Iceland Italy Multinational Sweden US	1 1 1 1 2 6 1 9
Hearing test	Poland	1
Macrocephaly	Australia Japan Norway US	1 1 1 1
Metabolic, Mitochondrial	Australia	1

Table F-3 Focus Area by Country and Number of Studies		
Focus Area	Country	Number of Studies
	France Ireland Portugal UK US	1 1 2 1 4
Neuroimaging	France Italy Netherlands Turkey US	1 1 1 1 3
Physical exam	US	7
Yield of work up	Multinational	1

Studies Reporting on Race and or Ethnicity

Studies performed in the US were more likely to report race and/or ethnicity of participants, especially medication trials.

Table F-4 Number of Studies Reporting Race and/or Ethnicity by Focus Area		
Focus Area	Reported	Not Reported
Associated Conditions	18	44
Diet and Dietary Tx	11	20
Medications	28	32
Work Up	20	56

Sample Size

The following table describes the sample size for studies in each DOH Focus Area. Studies of genetic testing and prevalence were larger than intervention studies and studies examining the yield of diagnostic evaluations. Prevalence studies often included population data. For genomic studies, large populations were necessary.

Table F-5 Sample Size by Focus Area						
Focus Area	<10	10-49	50-100	101-149	>150	Not reported
Associated Conditions	5	15	14	5	23	-
Diet and Dietary Tx, and novel Tx	2	19	2	3	5	-
Work-Up		16	26	3	29	2
Medications	3	41	7	3	6	-

Types of Studies

The association of specific medical conditions with ASD required prevalence and other epidemiologic approaches and thus descriptive studies and case control studies were included.

The utility of medical tests or evaluations as part of the diagnostic process for ASD is often evaluated using retrospective analyses. While not optimal, that is what is available for review and for decision making regarding recommendations regarding diagnostic evaluation. While descriptive studies were used to demonstrate the yield of specific tests, the role of medical characteristics in prediction of outcome or contribution to type of therapy requires prospective evaluation and is likely to be an area of research going forward.

Intervention studies were classified by randomized control trials, open label, and retrospective designs. Some open trials were included because they inform current practice. Many randomized, placebo controlled trials (RCT) include open label continuation to evaluation adverse effects and are listed as open label if reported separately. Single subject data was not included in the review of the medical literature.

Table F-6. Study Design by Focus Area – Associated Conditions						
Dental	Population sample					
	1					
GI	Population Sample	Retrospective	Prospective Cross-Sectional	Case Control		
	4	3	6	1		
Immunologic	Population Sample			Case Control	Registry	
	1			2	1	
Increased ASD Risk	Population Sample	Retrospective	Prospective Cross Sectional	Case Control	Registry	
	6	3	5	3	4	
Seizures*	Population Sample	Retrospective	Prospective	Case Series		*Meta-analysis
	2	4	5	1		1
Sleep			Prospective		Registry	
			8		1	2 papers from same sample

Table F-7. Study Design by Focus Area – Dietary and Novel Therapies						
	SBRCT	DBRCT	Cross Sectional, registry	Open label	Retrospective	Random Parallel Group
Diet	3	1	1			1
Obesity			1		2	
Supplements		8	4	7	1	
HBOT		2				

Table F-8. Study Design by Focus Area – Medication				
DBRCT	Open	Retrospective	Random Parallel Group	Secondary Analysis
31	19	9	1	2

Of the DBRCT trials, 4 had crossover design. Four also had open label continuation and placebo controlled discontinuation. Two of the reported open trials were open label continuations of DBRCTs.

Table F-9. Study Design by Focus Area - Etiologic Work Up					
Population Sample	Registries	Retrospective	Prospective Cross Sectional	Longitudinal	Reports on Same Registry
6	9	18	37	6	3

Multiple Reports on The Same Participants

Funded trials that collect and carefully evaluate participants often report on different aspects of the data or report sequentially as more participants are enrolled and additional evaluations performed. Examples include the Autism Genome Project (Annay 2012, 2012; AGP 2007; Klei 2012), Miles (2000,2005), Marcus, 2011, RUPP (2002,2005) and several studies using the Autism Treatment Network database. One reanalysis of data is included (Ip 2004; DeSoto, 2007). One meta-analysis is included.

F.5 Conclusion of Review

This review of the literature had the goals to acquire and evaluate the published, peer reviewed articles on medical evaluation of young children with ASD, comorbid conditions that should be considered in the assessment and care of these children, and medical interventions (including medication, supplements, and dietary interventions) that have been evaluated for children less than 8 years of age with ASD. Articles were included if they informed etiologic work up, reported on a medical condition that was important clinically relative to diagnosis, or presented treatment data beyond initial case reports or series that was informative for treatment.

In sum, there has been substantial progress in the biomedical evaluation and management of children with ASD in the 15 years since the initial report. There have been remarkable advances

in basic science since 1999 that resulted in many articles reporting on the identification of specific genes, use of technology to document neurobiologic differences, and biologic processes related to the pathophysiology of ASD. Diagnostic techniques such as chromosomal microarray were not available for clinical use until years after the 1999 NYSDOH ASD Guideline and are quickly being antiquated by even newer technology such as whole exome sequencing. One major influence has been from the recommendation of Chromosomal Microarray as a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. The number of genetic disorders associated with ASD has expanded greatly to include Fragile X syndrome, 15q11.2-11.3 duplication, Down syndrome, 16p 11.2 deletion, PTEN, Tuberous Sclerosis, Neurofibromatosis 1, Timothy syndrome, Smith Magenis syndrome, Cohen syndrome, Cole Hughes macrocephaly syndrome, Cornelia de Lange syndrome, Angelman syndrome, Williams syndrome, 17p11.2p11.2 duplication syndrome, 22q11.1 deletion syndrome, WAGR (Wilms tumor, aniridia), Duchenne muscular dystrophy, and Sotos syndrome, among others. Furthermore, specific genes associated with ASD have been identified on every chromosome.

The awareness that children with ASD were at risk for concurrent medical conditions was known in 1999, but the prevalence of comorbid conditions and impact on behavior and family functioning was not a topic of active study. Prevalence data documenting the occurrence of comorbid conditions were included because many of the topic areas are at the stage of confirmation of their association with ASD. Since comorbid conditions may impact intervention in childhood, the data supporting associations was reviewed to help clinicians understand what comorbid conditions to screen for in early childhood. Despite the literature on treatment still in development, in the 15 years since the 1999 NYSDOH ASD Guideline, the volume of evidence on medical conditions associated with ASD has been large, establishing associations with ASD that include sensory impairment (vision, hearing, auditory processing, olfaction, taste); sleep disorders (onset, maintenance, restless leg syndrome); GI disorders (constipation, diarrhea, pica, feeding and nutrition disorders, abdominal pain, leaky gut); neurologic disorders (seizures, tic disorders, catatonia, hypotonia, apraxia); metabolic disorders (Mitochondrial disorders, Smith Lemli Opitz syndrome, Disorder of Creatine metabolism, Sanfillipo syndrome); accidents (ingestions, drowning, wandering); and prematurity. Prenatal exposures associated with ASD including prenatal infection (CMV, Rubella) maternal exposures (valproate, misoprostol, thalidomide). Environmental factors that have been studied have included air pollution, mercury, and maternal immune response during pregnancy.

The use of medication as part of a behavioral treatment program was not as common place for younger children as it is now and many of the medications in common use were not commercially available. While complementary and alternative medicine was attractive to parents in 1999, the approaches with popular interest have changed over the years (Levy, 2015). Clinical researchers are applying conventional scientific evaluation of efficacy to both novel therapies and new uses of prescription medications (Anagostou and Hansen, 2011; Huffman, 2011).

In interpreting the results from this literature review, several limitations should be considered. First, studies completed on older children may hold true for younger children. If participants were not in the age group of concern, studies were not included, however. Second, criteria for ‘adequate evidence’ developed by the 1999 NYSDOH ASD Guideline panel exclude group studies without adequate control populations. However, for establishment of comorbidity descriptive studies were included in this review and nested case control studies within the diagnosis of ASD. Third, because the comorbidity of specific medical conditions that may impact success of intervention programs is important for clinicians and therapists since they may

impact the diagnostic suspicion of ASD and may impact therapy, studies whose control groups may not be the optimal choice were included. Children with developmental disabilities other than ASD will need to be examined for more accurate comparison of prevalence of comorbid conditions. Typical control groups from the areas from which children with ASD were ascertained are more appropriate than national statistics. In addition, genetic subtypes are likely to greatly impact interpretation of both medical comorbidity and intervention data in the future. Fourth, the 1999 NYSDOH ASD Guideline panel developed standard criteria to specify minimum quality and applicability standards for research studies providing adequate evidence about the efficacy of the evaluated intervention approach. For the large part, these criteria were the basis for the current report. Consequently, some potentially informative medical intervention studies (including CAM) may have been eliminated. Finally, additional relevant articles published after the review period, but before the panel meetings were added through a follow up search. Additional relevant literature was submitted as an amendment to the review process.

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Background

Review of published research evaluating outcomes associated with parent-mediated interventions 1999-2013

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Dietary Therapies and Obesity

A. Dietary Therapies

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C. Dietary Supplements

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<u>Novel Biomedical Therapies</u>

A. Hyperbaric oxygen

Doreen Granpeesheh a, Jonathan Tarbox a, Dennis R. Dixon a,*, Arthur E. Wilke Michael S. Allen a, James Jeffrey Bradstreet. Randomized trial of hyperbaric oxygen (2011)

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B. Medication

1. Alpha 1 Adrenergic Agents

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2. Amantadine

King, B.H., Wright, D.M., Handen, B.L., et al. (2001) Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. *Journal of the American Academy of Child & Adolescent Psychiatry. 40*(6), 658-665.

3. Antianxiety Agents

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5. Anticonvulsants

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6. Atypical Neuroleptics

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7. Donezapil

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8. Immunoglobins

Schneider, C.K., Melmed, R.D., Barstow, L.E., Enriquez, F.J., Ranger-Moore, J., Ostrem, J.A. (2006) Oral human immunoglobulin for children with autism and gastrointestinal dysfunction: a prospective, open-label study. *Journal of Autism and Developmental Disorders. 36*(8), 1053-1064.

9. Medication + Parent Management Training

Aman, M.G., McDougle, C.J., Scahill, L., et al. (2009) Medication and parent training in children with pervasive developmental disorders and serious behavior problems: results from a randomized clinical trial. *Journal of the American Academy of Child & Adolescent Psychiatry. 48*(12), 1143-1154.

10. Memantine

Chez, M.G., Burton, Q., Dowling, T., Chang, M., Khanna, P., Kramer, C. (2007). Memantine as Adjunctive Therapy in Children Diagnosed With Autistic Spectrum Disorders: An Observation of Initial Clinical Response and Maintenance Tolerability. *Journal of Child Neurology. 22*(5), 574-579.

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11. N Acetylcystine

Hardan, A.Y., Fung, L.K., Libove, R.A., et al. (2012) A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. *Biological Psychiatry. 71*(11), 956-961.

12. Secretin

Ratliff-Schaub, K., Carey, T., Reeves, G.D., Rogers, M.A. (2005). Randomized controlled trial of transdermal secretin on behavior of children with autism. *Autism. 9*(3), 256-265.

Roberts, W., Weaver, L., Brian, J., et al. (2001) Repeated Doses of Porcine Secretin in the Treatment of Autism: A Randomized, Placebo-Controlled Trial. *Pediatrics. 107*(5), e71.

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13. SNRI (Selective Norepinephrine Reuptake Inhibiters)

Arnold, L.E., Aman, M.G., Cook, A.M., et al. (2006) Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *Journal of the American Academy of Child & Adolescent Psychiatry. 45*(10), 1196-1205.

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Zeiner, P., Gjevik, E., Weidle, B. (2011). Response to atomoxetine in boys with high-functioning autism spectrum disorders and attention deficit/hyperactivity disorder. *Acta Paediatrica. 100*(9), 1258-1261.

14. SSRI (Selective Serotonin Reuptake Inhibiters)

DeLong, G.R., Ritch, C.R., Burch, S. (2002) Fluoxetine response in children with autistic spectrum disorders: correlation with familial major affective disorder and intellectual achievement. *Developmental Medicine and Child Neurology. 44*(10), 652-659.

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15. Stimulants

Jahromi, L.B., Kasari, C.L., McCracken, J.T., et al. (2009) Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. *Journal of Autism and Developmental Disorders. 39*(3), 395-404.

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16. Tricyclic Antidepressants

Bhatti, I., Thome, A., Smith, P.O., et al. (2013) A retrospective study of amitriptyline in youth with autism spectrum disorders. *Journal of Autism and Developmental Disorders. 43*(5), 1017-1027.

Coskun, M., Karakoc, S., Kircelli, F., Mukaddes, N.M. (2009) Effectiveness of mirtazapine in the treatment of inappropriate sexual behaviors in individuals with autistic disorder. *Journal of Child & Adolescent Psychopharmacology. 19*(2), 203-206.

Posey, D.J., Guenin, K.D., Kohn, A.E., Swiezy, N.B., McDougle, C.J. (2001) A naturalistic open-label study of mirtazapine in autistic and other pervasive developmental disorders. *Journal of Child & Adolescent Psychopharmacology. 11*(3), 267-277.

Etiologic Work Up

A. EEG (also see Seizures)

Shevell, M.I., Majnemer, A., Rosenbaum, P., Abrahamowicz, M. (2001) Etiologic yield of autistic spectrum disorders: a prospective study. *Journal of Child Neurology. 16*(7), 509-512.

B. Exposures and Toxicity

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