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Diagnostic Accuracy of Primary Care Clinicians Across a Statewide System of Autism Evaluation

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Abstract

Objective—To evaluate the diagnostic accuracy of the Early Autism Evaluation (EAE) Hub system, a statewide network that provides specialized training and ongoing collaborative support to community primary care providers (PCP) in the diagnosis of young children at risk for autism spectrum disorder (ASD).

Methods—EAE Hub clinicians referred a consecutive sample of children, ages 14–48 months, to this prospective diagnostic study for blinded follow-up expert evaluation including assessment of developmental level, adaptive behavior, and ASD symptom severity. The primary outcome was agreement on categorical ASD diagnosis (present/absent) between EAE Hub clinician (index diagnosis) and ASD expert (reference standard).

Results—Among 126 children (mean age: 2.6 years; 77% male; 14% Latinx; 66% non-Latinx White), 82% (n=103) had consistent ASD outcomes between the index and reference evaluation. Sensitivity was 81.5%, specificity was 82.4%, positive predictive value was 92.6%, and negative predictive value was 62.2%. There was no difference in accuracy by EAE Hub clinician or site. Across measures of developmental and adaptive skills, there were significant differences between

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Contributors Statement Page

Drs. Rebecca McNally Keehn and Brandon Keehn conceptualized and designed the study, designed the data collection instruments, led data collection, analysis, and interpretation, drafted the initial manuscript, and reviewed and revised the manuscript for important intellectual content.

Drs. Nancy Swigonski, Patrick Monahan, and Mary Ciccarelli contributed to data analysis and interpretation efforts and reviewed and revised the manuscript for important intellectual content.

Drs. Brett Enneking, Tybytha Ryan, Ann Marie Martin, Lisa Hamrick, and Girija Kadlaskar and Ms. Angela Paxton contributed to acquisition of data and reviewed and revised the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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true positive (TP) and false negative (FN) cases (all *P*s<0.001; Cohens *d*=1.1–1.4), with TP cases evidencing greater impairment.

Conclusions—Community-based primary care clinicians who receive specialty training can make accurate ASD diagnoses in most cases. Diagnostic disagreements were predominately FN cases in which EAE Hub clinicians had difficulty differentiating ASD and global developmental delay. FN cases were associated with a differential diagnostic and phenotypic profile. This research has significant implications for the development of future population health solutions that address ASD diagnostic delays.

Article Summary:

This prospective study examines the diagnostic accuracy of community-based PCPs trained as part of a statewide system of autism evaluation.

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder defined by impairments in social communication and the presence of restricted and repetitive behaviors[1] with estimated prevalence of 1 in 36 8-year-old children.[2] While reliable ASD diagnosis is often possible in the second year of life,[3] the median age of diagnosis in the US is 49 months.[2] For many children, this delay[4–6] is due to a bottleneck in access to diagnostic evaluations.[7] Shortages of specialists[8] trained to provide diagnostic evaluations and clustering of available specialists in metropolitan areas[9–11]result in excessive family travel requirements, lost wages, and need to find alternative caregivers for other children or dependents.[12–15] Further, labor- and cost-intensive evaluation models and assessment tools limit efficiency and contribute to organizational[16–18] and family[19] burden. These factors, together with systemic influences on socioeconomic status, cultural stigma, and reduced access to information, education, and community resources, contribute to substantial diagnostic disparities for historically minoritized children and families.[20–22] ASD diagnostic delays impede enrollment in targeted interventions with cascading individual[23–25] and societal[26–28] consequences. As such, finding feasible, equitable, and scalable solutions that address ASD diagnostic delays and disparities is a public health imperative.

In recent years, tension between the notion that ASD diagnostic evaluation must be expert-driven in order to maintain quality standards[29] and the very significant demands for increasing capacity of diagnostic service systems[18] has grown. Yet, there seems to be increasing recognition that tiered community-based approaches that enhance the capacity of primary care providers (PCP) to conduct diagnostic evaluations of young children at risk for ASD hold promise for reducing delays and disparities.[30,31] Both the American Academy of Pediatrics (AAP)[32] and the Canadian Pediatric Society[33] now recognize that general pediatricians with training in application of DSM-5 ASD criteria can make a clinical diagnosis of ASD. While non-specialist providers such as PCPs will not have the expertise to make a definitive diagnosis for all at risk children (i.e., given the substantial heterogeneity of the disorder), there is mounting evidence to suggest that PCPs can make an initial clinical diagnosis to facilitate initiation of services for many young children with clear ASD symptoms.[18,30,31,34]

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Data on the implementation of novel diagnostic technologies[35,36] and streamlined training[30] and evaluation models[37–40] is emerging rapidly. Findings suggest that these innovative diagnostic approaches may shift clinician knowledge and perceived competency, improve access, and result in moderate to high degree of diagnostic accuracy. However, studies on PCP training in ASD diagnosis have been limited by small sample sizes, variable methodological quality, and heterogenous design and selection of outcome variables.[30] Guan et al[30] recently called for more rigorous studies of PCP evaluation models that include demographic characteristics of clinicians and patients, comprehensive assessments of outcome, and data on diagnostic accuracy.

Community-based, PCP-delivered ASD diagnostic evaluation models have high potential to reduce diagnostic delays and disparities. As such, our goal in the present prospective diagnostic study was to evaluate the diagnostic accuracy of a statewide model of early ASD evaluation in the primary care setting. Specifically, we present indices of diagnostic accuracy between PCPs trained to deliver ASD evaluations and comprehensive expert ASD evaluation, as well as differences in diagnostic, demographic, and phenotypic characteristics across diagnostic accuracy groups.

Methods

Study Setting

This study took place within the Early Autism Evaluation (EAE) Hub system, a statewide network of community PCPs trained to provide streamlined diagnostic evaluations for young children, ages 14–48 months, at risk for ASD.[39] As outlined in McNally Keehn et al,[39] EAE Hub clinician training involved didactics in ASD evaluation of young children as well as a clinical practicum with practice based-coaching until mastery of all components of the standard clinical diagnostic evaluation was achieved. Following initial training, all PCPs participated in a longitudinal learning collaborative (which meets virtually every month) with content on challenging case presentations, updated ASD diagnosis and care management practice standards, billing and coding guidance, and information on statewide ASD resources. EAE Hubs receive referrals from regional PCPs for evaluation of children determined to be at-risk for ASD based on surveillance and/or developmental screening and then follow a standard clinical evaluation protocol including administration/review of standard developmental and autism screening tools (i.e., Ages and Stages Questionnaire-3 and Modified Checklist for Autism in Toddlers – Revised with Follow-Up), a DSM-5 focused developmental history and clinical interview, physical examination, and administration of an observational assessment of ASD (Screening Tool for Autism in Toddlers [41]). The EAE Hub clinician then issues a best-estimate ASD diagnosis and report with clinical recommendations, including information on community and statewide interventions and resources for children with ASD and developmental disabilities.

Study Design & Participants

Standards for Reporting Diagnostic Accuracy (STARD) guidelines were followed in the design and conduct of this prospective diagnostic study. Seven EAE Hubs set within primary care practices (i.e., including six large health system group practices and one private

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practice) referred children, ages 14–48 months evaluated for ASD in the community primary care setting, to the study between June 2019 and August 2022. To be included, children were age 14–48 months at time of EAE Hub evaluation and had an English-speaking primary caregiver/guardian. This study was approved by the University Institutional Review Board, and written informed consent was obtained from legal guardians of all participants.

Study Procedure

EAE Hubs were recruited into the study in a non-random staggered manner during the study period; site startup was impacted by COVID-19 institutional research and patient care regulations. Each site referred a prospective, consecutive sample of children who received an EAE Hub evaluation following site startup until approximately 20 children from each site were enrolled (note: Site 1 recruited a greater number of participants as they served as a pilot and study site; Site 4 recruited fewer participants due to relocation of the EAE Hub clinician during the study period). This recruitment procedure allowed the study team to maintain diagnostic blindness and assess children with both ASD and non-ASD outcomes without referral bias. During EAE Hub evaluations, clinicians (or a member of the EAE Hub clinical team; e.g., nurse or medical assistant) provided caregivers of children evaluated with a study brochure, brief verbal description of the study, and obtained signed consent to share contact information with the study team for recruitment and enrollment. Once enrolled, an electronic caregiver-report survey (i.e., caregiver-reported demographic data on child race/ethnicity and caregiver/family income and education level) and EAE Hub evaluation data (i.e., index ASD diagnosis and clinician diagnostic certainty) were collected by a member of the study team (see Figure 1). The study team, consisting of a licensed clinical psychologist (RMK, BE, or TR) with expertise in evaluation of ASD in toddlers and young children and clinical research technician (advanced graduate student or postdoctoral fellow: GK, LH, or AMM), traveled to the EAE Hub to conduct a follow-up gold-standard ASD diagnostic assessment within 16 weeks of the initial EAE Hub evaluation. Figure 1 and eMethods detail the outcome measures, including child, caregiver, and clinician measures, administered to obtain a best-estimate ASD diagnosis (reference standard diagnosis). Participants were compensated with a gift card in the amount of $25 per hour of completed research evaluation (up to a maximum of $75).

Analysis

Data analyses were performed using SPSS (IBM SPSS Statistics, Version 28, Armonk, NY: IBM Corp) and JMP (JMP®, Version 13.0, Cary, NC: SAS Institute Inc.). Continuous variables are reported as means and standard deviations, and categorical variables are reported as absolute frequencies and percentages. Diagnostic accuracy, the primary outcome of interest, was calculated by comparing percent agreement between the EAE Hub diagnosis and ASD-specialist on categorical ASD diagnosis (ASD; non-ASD). Chance- corrected agreement (kappa) and accuracy indices of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) and the 95% confidence interval (CI) are reported. There were no missing data or indeterminate results regarding index or reference diagnoses. Variability in diagnostic accuracy by EAE Hub site and clinician was examined via a series of Chi-square and Fishers Exact tests. Exploratory post-hoc analyses were conducted to examine diagnostic, demographic, and phenotypic differences between true

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positive (TP) and false negative (FN) outcome groups to understand differences between children who were correctly diagnosed with ASD versus those who were missed (or unable to be definitively diagnosed) by non-specialist clinicians. Chi-square and two-sided t-tests were used to compare categorical and continuous variables, respectively. Finally, an additional subset analysis of accuracy indices for cases with EAE Hub clinician diagnostic certainty ratings of Highly or Completely Certain was conducted to examine whether agreement improved based on clinician perceptions of diagnostic confidence. A sample size of N=126 provided an upper/lower limit 95% CI width of 0.067 for overall diagnostic agreement, assuming 82% agreement (i.e., as observed in this study).

Results

Participant flow through the study is detailed in Figure 2. Of 182 referred children, 131 enrolled, and index and reference standard diagnosis evaluations were included in the final analysis for 126 children across 6 EAE Hubs. Ten clinicians conducted a mean of 12.6 (SD=7.4) evaluations (eTable 1 for EAE Hub clinician demographics and learning collaborative participation). Mean age of children was 2.6 years; 77% (n=97) were male, 14% (n=18) were Hispanic/Latinx, and 66% (n=84) were non-Latinx White (Table 1). Across all children evaluated, scores on measures of developmental and adaptive skills fell well below the average range and ASD symptom severity was in the moderate range.[42] Seventy-five percent (n=94) of children had a reference diagnosis of ASD; 10% had GDD (n=13), 10% had LD (n=13), and 5% (n=6) had another emotional, behavioral or medical concern (n=6).

Agreement between Index and Reference Diagnosis

Of 126 children evaluated, ASD diagnosis was consistent between the EAE Hub evaluation (index diagnosis) and expert research evaluation (reference diagnosis) for 82% (n=103) of cases (Table 2). Chance-corrected diagnostic agreement was moderate, K=0.580 (95% CI, 0.429–0.731). Sensitivity, or correct classification of ASD diagnosis, was 81.5% (95% CI, 72.4–88.1) while specificity, or correct classification of non-ASD diagnosis was 82.4% (95% CI, 66.5–91.7). Positive predictive value (PPV) was 92.6% (95% CI, 84.8–96.6) and negative predictive value was 62.2% (95% CI, 47.6–74.9). Overall, 60% (n=75) of cases were True Positive (TP: index=ASD; reference=ASD), 5% (n=6) were False Positive (FP: index= ASD; reference-non-ASD), 22% (n=28) were True Negative (TN: index=non-ASD; reference=non-ASD), and 14% (n=17) were False Negative (TN: index=non-ASD; reference= ASD; Table 2).

Diagnostic Agreement by EAE Hub Site and Clinician

There was no difference between EAE Hub sites in overall accuracy (i.e., accurate versus not; TP + TN vs. FP + FN; P=.89) or proportion of FN (compared to TP) cases (P=.67; eTable 2). Similarly, there was no difference in overall accuracy (P=.24) or proportion of FN cases (P=0.09) by EAE Hub clinician for those submitting data for ≥ 5 children (n=8).

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Diagnostic, Demographic and Phenotypic Differences by Diagnostic Agreement Group

Descriptive, clinical, and phenotypic data by diagnostic group can be found in eTable 3. To address the question of what diagnostic, demographic, and/or phenotypic factors may be associated with false negative diagnoses made by trained PCPs, we conducted an exploratory analysis of differences between TP and FN cases (Table 3). There was a significant difference in dichotomized (i.e., Highly or Completely Certain vs. all other ratings) index clinician diagnostic certainty ratings between TP and FN groups, P=0.002, with a higher proportion of Highly-Completely Certain ratings for the TP (95%; 71/75), as compared to FN (65%; 11/17) group. Similarly, index clinicians flagged a significantly higher proportion of FN cases (69% of FN; 17% TP) for specialty follow-up evaluation, P=<.001. There were no demographic differences by age or sex (Ps>.20). Across measures of developmental and adaptive skills (i.e., Mullen Scales of Early Learning Verbal Developmental Quotient [DQ], Nonverbal DQ, and Early Learning Composite; Vineland-3 Adaptive Behavior Composite), there were significant differences between TP and FN cases (all Ps<0.001), with the TP group evidencing significantly greater impairment as compared to the FN group. There was no significant difference between ADOS-2 Calibrated Severity Scores between the TP and FN groups (P=0.28) suggesting no meaningful differences in ASD symptom severity between groups. To address factors that may be associated with false positive diagnoses, we examined differences between TN and FP cases (eTable 4). Although these results must be interpreted with substantial caution given small sample size, it appears that there may be a trend toward older age in the FP group.

Subset Analysis by Index Diagnostic Certainty Ratings

Among the subset of cases in which EAE Hub clinician rated diagnostic certainty to be Highly or Completely Certain (N=105), sensitivity was 84.5% (95% CI, 75.3–90.7) and specificity was 90.5% (95% CI, 71.1–97.3). Positive predictive value (PPV) was 97.3% (95% CI, 90.5–99.2) and negative predictive value was 59.4% (95% CI, 42.3–74.5).

Discussion

In this prospective diagnostic study, we found 82% agreement between trained primary care clinicians and blinded expert research evaluation on categorical ASD diagnosis of children ages 14–48 months. Accuracy indices of sensitivity, specificity and PPV were high (i.e., 81.5, 82.4, and 92.6% respectively), while NPV was substantially lower (i.e., 62.2%). There were no statistically significant differences in accuracy by EAE Hub site or clinician. Diagnostic disagreements were predominately FN cases in which EAE Hub clinicians had difficulty differentiating ASD and global developmental delay. Clinicians flagged most of these cases for follow-up specialty evaluation. FN (as compared to TP) cases were associated with a differential diagnostic and phenotypic, but not demographic, profile. When analysis was restricted to cases in which EAE Hub clinicians rated their diagnostic certainty high, measures of sensitivity, specificity, and PPV improved. To our knowledge, this is the largest study to date that evaluates diagnostic accuracy of a coordinated system of diagnosis in the primary care setting. Notable strengths of this study include the diversity of included primary care index clinicians (i.e., from large health system group practices, federally-qualified health centers, and private practices) and children evaluated (i.e., from

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low socioeconomic and family education backgrounds), large sample size, and rigorous methodology (i.e., including blinded reference standard evaluations).

While existing reports of primary care based models of ASD diagnosis show promising evidence for improved service access and acceptable accuracy, studies have been limited by small sample size and reduced methodological rigor or have not used a standard approach for training and diagnostic evaluation.[30] Nonetheless, our 82% diagnostic agreement between index and reference diagnosis is comparable to that of others who have reported rates of agreement between PCP and expert evaluation between 71 and 85%.[34,43,44] Importantly, across EAE Hub sites and clinicians, including primary care physicians and nurse practitioners, there was no difference in overall accuracy or rate of FN cases. Given the small number of NPs in our study, future examination of accuracy with a larger sample of diverse clinicians is needed.

Our study is the first to report on ASD accuracy metrics between non-specialist clinicians and expert diagnosis when a standard training and clinical pathway is followed. Findings suggest that PCPs who receive specialty training are highly reliable when they confirm an ASD diagnosis, as evidenced by our very low rate of FP cases (6%) and high PPV (92.6%). Clinicians were unable to make a definitive diagnosis or missed ASD in 14% of cases, resulting in low NPV (62.2%). Similar to the findings of Penner et al.,[34] FN cases evidenced higher verbal and nonverbal developmental level and adaptive skills, though most in our study still met criteria for global developmental delay. Notably, there was no difference in ASD symptom severity between TP and FN cases, suggesting that index clinicians may place more emphasis on developmental impairment than ASD-specific symptoms when making diagnostic decisions. FN cases were associated with lower index clinician diagnostic certainty and higher rates of referral (69% of cases) for specialty evaluation, suggesting that clinicians recognized that these children demonstrated a more complex profile making differential diagnosis between global developmental delay and ASD challenging. When analysis of diagnostic agreement was restricted to only cases for which index diagnostic certainty was high, sensitivity, specificity, and PPV increased, suggesting that primary care clinicians perceive their ability to render a correct ASD diagnosis with high accuracy. Future research should evaluate whether triaging cases for specialty evaluation based upon the child's overall developmental level (i.e., those with higher developmental skills) and/or low clinician diagnostic certainty may mitigate the rate of FN diagnosis in the primary care setting.

Limitations

A primary limitation of the present study is the high proportion (75%) of reference ASD diagnosis in the sample, resulting in low sample size for comparisons by accuracy subgroup. Due to small sample size, we did not use modeling approaches to adjust for potential correlated outcomes of patients clustered within EAE Hub sites or clinicians; however, we did examine site and clinician differences on overall accuracy and proportion of FN cases, and results were not significant. We also did not collect data on those children evaluated in the EAE Hub system who did not consent to participate, and thus we cannot rule out unmeasured bias in our findings or confirm the generalizability of our findings to all young

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children who require ASD evaluation. Inclusion of only children with English-speaking caregivers limits the generalizability of our findings and further solutions to ensure equitable access to diagnostic evaluations are necessary. Although we asked clinicians to flag children that required specialty follow-up evaluation, we designed the study to force index clinicians to make a binary (ASD present/absent) choice about ASD outcome, perhaps artificially deflating accuracy indices due to caution against overdiagnosis. Finally, although an initial ASD diagnosis is needed to access specific services, longitudinal developmental evaluation is important for individualized intervention and prognosis planning.[45] As such, tiered diagnostic approaches represent an important and promising solution to one component of the larger ASD service bottleneck problem.

Conclusion

Tiered diagnostic approaches, including primary care-based models such as the EAE Hub system, are now being tested as one solution to address the need for increased ASD diagnostic evaluation capacity.[18,31] The EAE Hub system was developed with the primary goal of lowering the age of ASD diagnosis through providing streamlined access to localized diagnostic evaluation within the primary care setting. We have previously shown that the EAE Hub model, which involves intensive training for PCPs in ASD diagnosis and ongoing participation in a longitudinal learning collaborative, is feasible[39] with over 4000 children evaluated since 2012. In the present prospective diagnostic study, we extend the empirical support for this model by demonstrating a high level of diagnostic accuracy (i.e., 82%) in a sample of diverse community PCPs and at-risk children. Additional research is needed to understand implementation promotors and barriers to broad scale up of community-based ASD models, as well as replication and comparative effectiveness studies that allow for determination of the key components of training and model implementation necessary for success. Testing strategies aimed to mitigate false negative cases will be an essential next step in ensuring the accuracy and quality of streamlined community-based ASD evaluations. Further, it will be critical to develop and test adaptations of tiered diagnostic approaches for non-English speaking children as well as to determine whether these types of models lead to earlier intervention enrollment, both efforts currently underway in the EAE Hub system. Collectively, the study of innovative diagnostic models has important implications for how future population health solutions that address the ASD diagnosis crisis are designed and implemented. ASD experts, self-advocates and families, and other health service stakeholders (i.e., insurers, service providers) must work together to construct and put into action flexible, evolving, evidence-driven health policies that account for scientific innovation and advancements in ASD diagnosis.[46,47]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement:

Deidentified individual participant data has been shared as part of the National Institute of Mental Health Data Archive (NDA).

Abbreviations:

(AAP)	American Academy of Pediatrics
(ADOS-2)	Autism Diagnostic Observation Schedule, Second Edition
(ASD)	autism spectrum disorder
(CI)	confidence interval
(DQ)	developmental quotient
(EAE)	Early Autism Evaluation
(FN)	false negative
(FP)	false positive
(NPV)	negative predictive value
(PPV)	positive predictive value
(PCP)	primary care provider
(STARD)	Standards for Reporting Diagnostic Accuracy
(TN)	true negative
(TP)	true positive

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What's Known on This Subject:

Finding effective and scalable solutions to address ASD diagnostic delays and disparities is a public health imperative. Tiered community-based approaches that enhance the capacity of primary care clinicians to provide diagnostic evaluations hold promise for addressing this problem.

What This Study Adds:

Primary care clinicians trained as part of a statewide system can make accurate ASD diagnoses in a majority of cases, extending evidence that tiered community-based models may be a valid approach for reducing ASD diagnostic delays.

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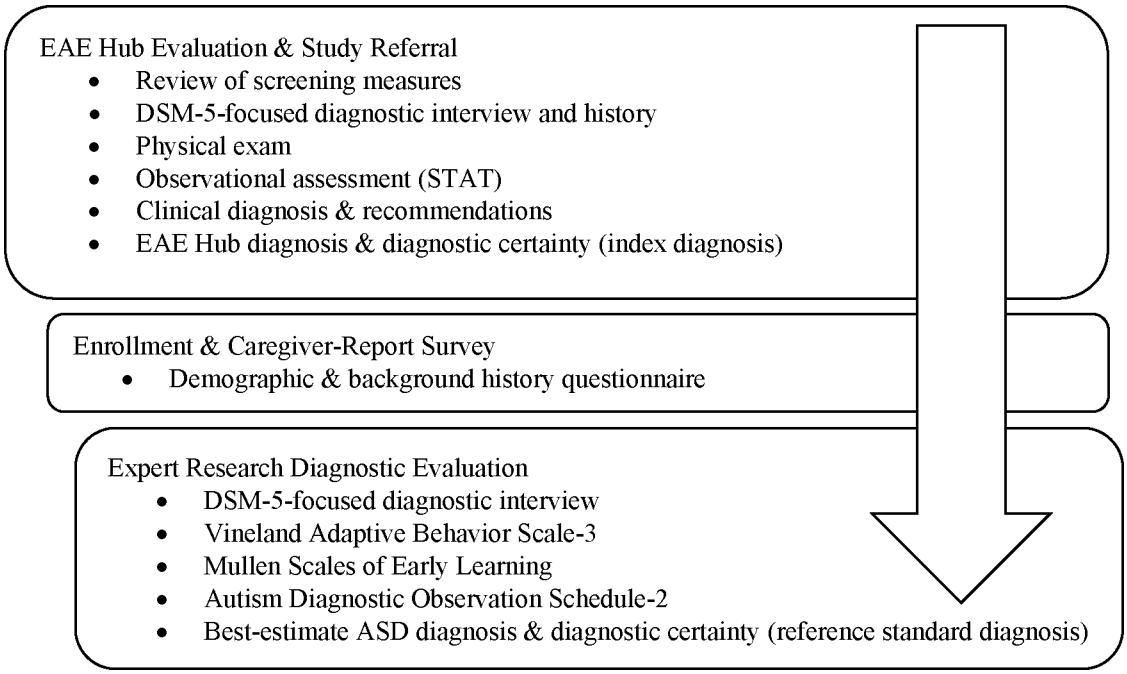

Figure 1.
Study Procedure

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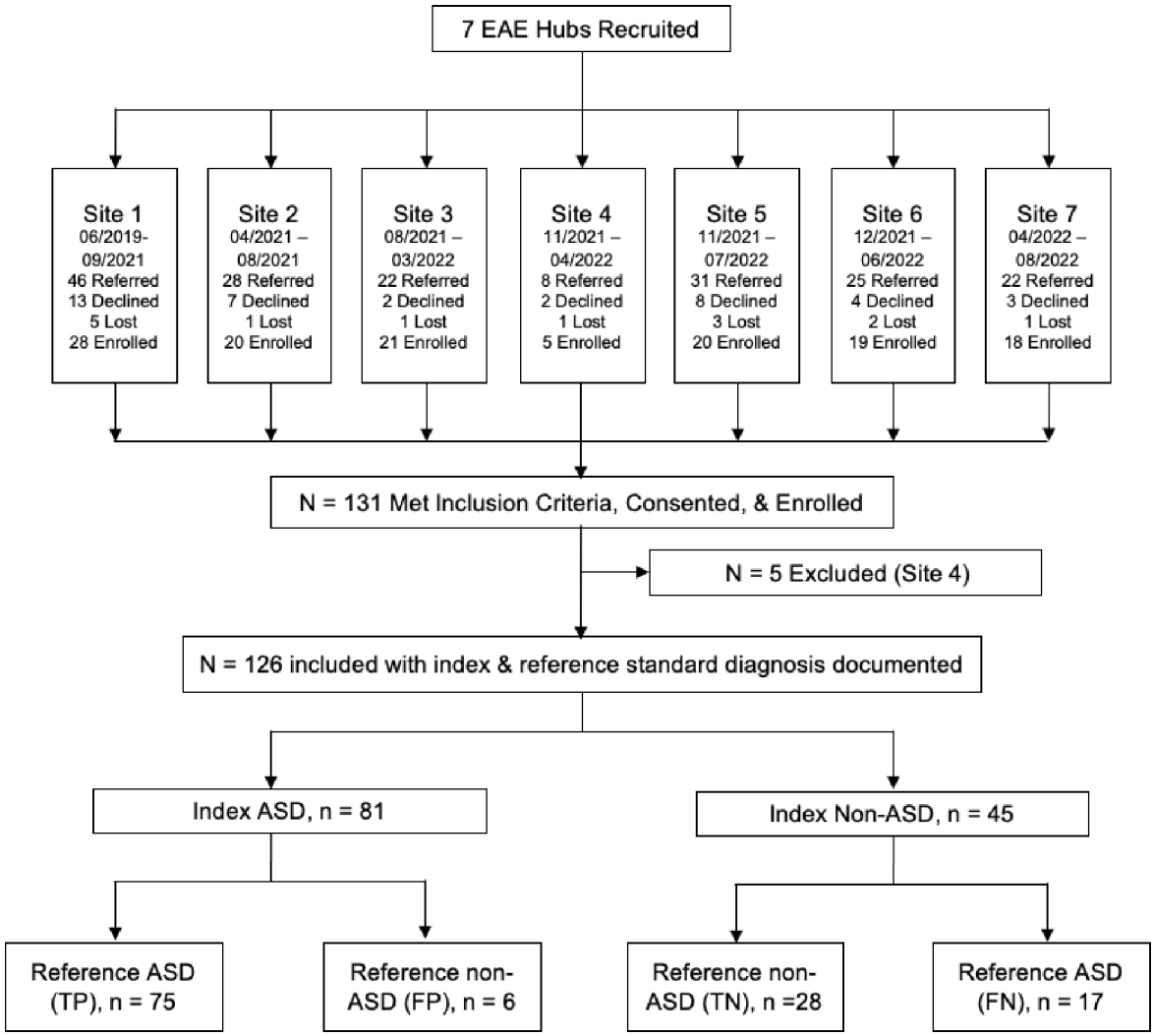

Figure 2.

EAE Hub site and participant flow through the study. Site 1 served as a pilot and study site, resulting in > 20 participants referred. Site 4 ended recruitment prior to meeting criterion due to relocation of the EAE Hub clinician during the study period. Startup and recruitment duration for some sites was impacted by COVID-19 institutional research and patient care regulations.

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Table 1

Child Demographics and Clinical Characteristics

	All Included N (%)
Number participants	126
Age, m (SD) in months	2.6 (0.6)
Sex	
Male	97 (77)
Female	29 (23)
Race/Ethnicity	
>1 race	7 (6)
Asian	1 (1)
Black	10 (8)
Hispanic/Latinx, any race	18 (14)
White	84 (66)
Unknown/Not reported	6 (5)
Yearly household income	
< $25,000	21 (17)
$25,000–49,999	40 (32)
$50,000–74,999	29 (23)
$75,000–99,000	12 (10)
$100,000–149,999	13 (10)
>$150,000	2 (2)
Primary caregiver education level	
< High school diploma	8 (6)
High school diploma/GED	36 (29)
Some college, no degree	32 (25)
Associate degree/postsecondary certificate	14 (11)
Bachelor's degree	24 (19)
Graduate degree	12 (10)
MSEL ELC, m (SD)	61.8 (14.7)
MSEL Nonverbal DQ, m (SD)	70.4 (17.3)
MSEL Verbal DQ, m (SD)	52.1 (24.2)
Vineland-3 ABC, m (SD)	67.9 (12.0)
ADOS-2 CSS, m (SD)	7.0 (3.0)
Reference diagnosis of ASD	94 (75)
Reference diagnosis of GDD	13 (10)
Reference diagnosis of LD	13 (10)
Reference diagnosis of Other[a]	5 (4)
Reference diagnosis of known genetic syndrome	1 (1)

Abbreviations: ADOS-2 CSS, Autism Diagnostic Observation Schedule, Second Edition Calibrated Severity Score; ASD, autism spectrum disorder; DQ, developmental quotient; GDD, global developmental delay; LD, language delay, MSEL ELC, Mullen Scales of Early Learning Early Learning Composite; Vineland-3 ABC, Vineland Adaptive Behavior Scales, Third Edition Adaptive Behavior Composite.

[a]Other diagnosis includes emotional behavioral concerns such as separation anxiety, sensory processing impairment, parent-child relational problem.

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Table 2

Agreement between Index and Reference Diagnosis (N=126)

		Reference Standard Diagnosis	
		ASD	**Non-ASD**
Index Diagnosis	ASD	75 (60)	6 (5)
	Non -ASD	17 (14)	28 (22)

Data represented as number (%).

Index diagnosis is based on EAE Hub evaluation. Reference standard diagnosis based on blinded expert research diagnosis.

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Table 3

Diagnostic, Demographic, and Phenotypic Differences between True Positive and False Negative Cases

	TP n=75	FN n=17	*P*	Effect Size
Clinical Characteristics				
Index Diagnostic Certainty, n (%)			.002	9.7
Completely/Highly certain	71 (95)	11 (65)		[2.4-39.9][a]
All other ratings	4 (5)	6 (35)		
Specialty Evaluation, n (%)			<.001	10.6
Referral not recommended	58 (83)	5 (31)		[3.1-36.2][a]
Referral Recommended	12 (17)	11 (69)		
Demographic Characteristics				
Age, m (SD) years	2.7 (0.6)	2.7 (0.6)	.89	0.04[b]
Sex, n (%)			.20	2.1
Male	63 (84)	12 (71)		[0.7-7.4][a]
Female	12 (16)	5 (29)		
Phenotypic Characteristics				
MSEL, m (SD)				
Verbal DQ	39.8 (17.9)	60.1 (18.7)	<.001	1.4[b]
Nonverbal DQ	63.0 (15.4)	78.7 (10.8)	<.001	1.1[b]
MSEL ELC	54.7 (7.6)	64.5 (12.0)	<.001	1.1[b]
Vineland-3 ABC, m (SD)	62.3 (9.6)	72.1 (4.8)	<.001	1.1[b]
ADOS-2 CSS, m (SD)	8.6 (1.6)	8.1 (2.0)	.28	0.3[b]

Abbreviations: ADOS-2 CSS, Autism Diagnostic Observation Schedule, Second Edition Calibrated Severity Score; ASD, autism spectrum disorder; DQ, developmental quotient; False Negative (FN); False Positive (FP); GDD, global developmental delay; LD, language delay, MSEL ELC, Mullen Scales of Early Learning Early Learning Composite; Vineland-3 ABC, True Negative (TN); True Positive (TP); Vineland Adaptive Behavior Scales, Third Edition Adaptive Behavior Composite.

Index diagnosis is based on EAE Hub evaluation.

Categorical variables presented as number (%); continuous variables presented as mean (SD).

P values represent 2-sided significance of *t*-test for continuous variables and Chi-square or Fisher's Exact Test for categorical variables.

[a] Effect sizes are reported as Odds Ratio [95% CI]

[b] or Cohen's *d*.