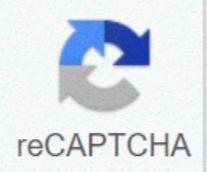




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Ados module 3 sample report

Searching for a minimal set of behaviors for autism detection through feature selection-based machine learning Your article has downloaded Charlotte Küpper, Sanna Stroth, ... Stefan Roepke Nicole Wolff, Gregor Kohls, ... Veit Roessner Halim Abbas, Ford Garberson, ... Dennis P. Wall Suma Jacob, Jason J. Wolff, ... Jed T. Elison Wai M. Hassan, Abeer Al-Dbass, ... Afaf El-Ansary Jonathan T. Megerian, Sangeeta Dey, ... Sharief Taraman Laurent Mottron & Danilo Bzdok Jérémie Lefort-Besnard, Kai Vogeley, ... Danilo Bzdok Bokan Bao, Javad Zahiri, ... Eric Courchesne Although the prevalence of autism spectrum disorder (ASD) has risen sharply in the last few years reaching 1 in 68, the average age of diagnosis in the United States remains close to 4, well past the developmental window when early intervention has the largest gains. This emphasizes the importance of developing accurate methods to detect risk faster than the current standards of care. In the present study, we used machine learning to evaluate one of the best and most widely used instruments for clinical assessment of ASD, the Autism Diagnostic Observation Schedule (ADOS) to test whether only a subset of behaviors can differentiate between children on and off the autism spectrum.

Study group	Baseline ADOS module (rows)	Evaluation ADOS module (columns)			Module changes ^a		Number of module (intervention vs. comparison group)	
		1	2	3	n	%		
Intervention group	1	44	18	13	39	58.2	28	41.8
	2	23	0	10	13		12,2 = 7	2.0 [0.7, 4.0], p = 2
	3	0	0	0	0			
Comparison group	1	9	5	2	14	53.8	12	46.2
	2	17	0	10	10			
	3	1	0	0	1			

^aNote: ADOS = Autism Diagnostic Observation Schedule. Odds ratios (OR) were obtained using univariate and multivariable logistic regression analyses.

^bNumber of ADOS modules used as features and validation. 18 derived by developmental delay and 17 derived as broader than child and

ADOS relies on behavioral observations in a clinical setting and consists of four modules, with module 2 reserved for individuals with some vocabulary and module 3 for higher levels of cognitive functioning. We ran eight machine learning algorithms using stepwise backward feature selection on score sheets from modules 2 and 3 from 4540 individuals. We found that 9 of the 28 behaviors captured by items from module 2, and 12 of the 28 behaviors captured by module 3 are sufficient to detect ASD risk with 98.27% and 97.66% accuracy, respectively. A greater than 55% reduction in the number of behaviors with negligible loss of accuracy across both modules suggests a role for computational and statistical methods to streamline ASD risk detection and screening. These results may help enable development of mobile and parent-directed methods for preliminary risk evaluation and/or clinical triage that reach a larger percentage of the population and help to lower the average age of detection and diagnosis. Rates of autism spectrum disorder (ASD) continue to climb, now impacting 1 in 68 individuals in the United States.¹ Despite important progress in understanding the genetics of ASD,^{2,3} ASD remains diagnosed through behavioral examination. The diagnosis of ASD is currently made using instruments designed to measure impairments in the two core domains of ASD, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V): (1) communication and social interaction and (2) restricted interests and repetitive behaviors.

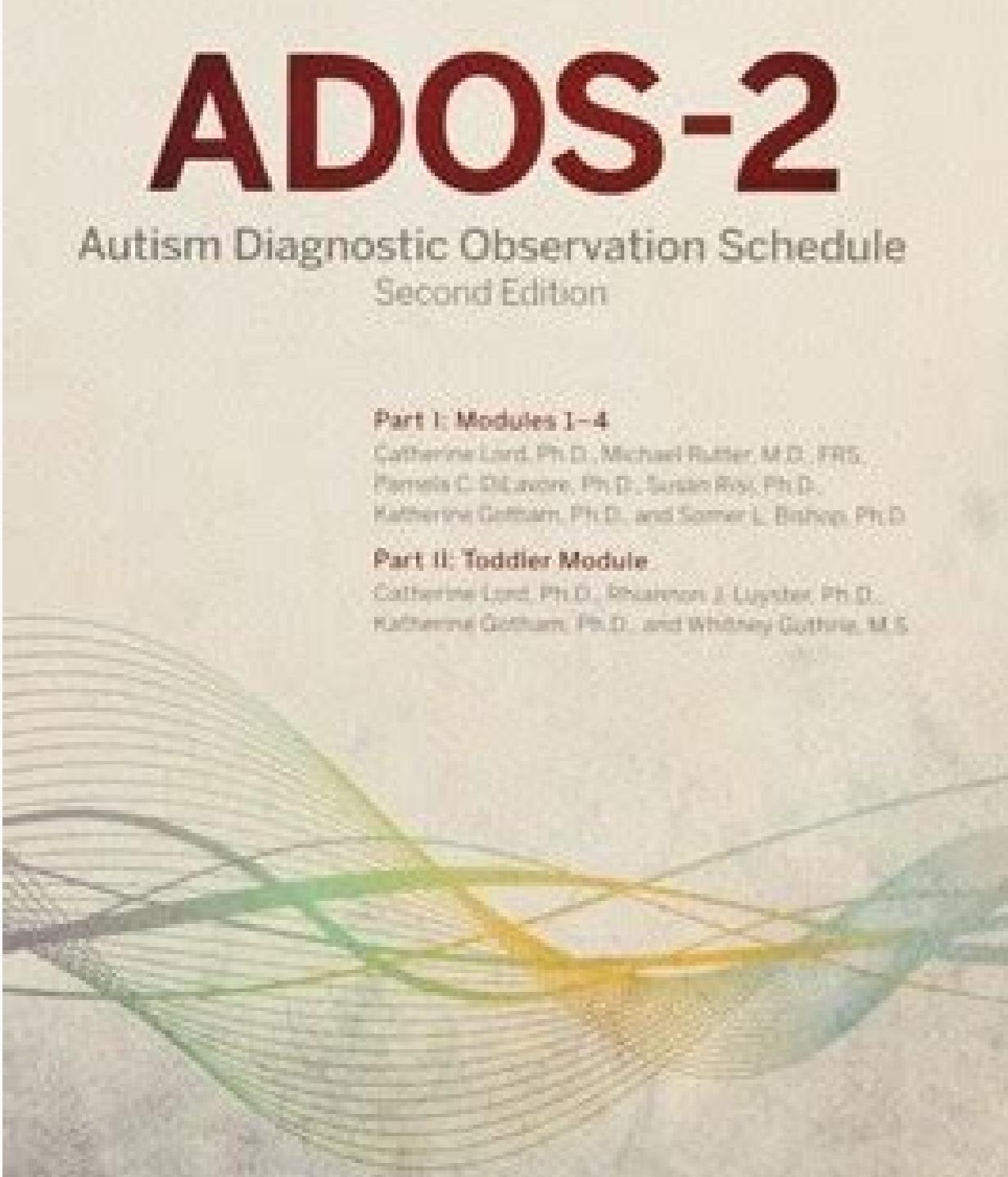


The Autism Diagnostic Observation Schedule (ADOS)⁴ is one of the most widely used instruments to assist in ASD diagnosis. The ADOS consists of a series of semi-structured activities designed to elicit specific behaviors of social interaction, communication, imaginative use of objects, restricted interests and repetitive behaviors. The diagnostic test is split into four modules, each tailored to specific individuals based on their language and developmental level to ensure coverage of a diverse set of behavioral manifestations.⁴ A certified professional at a clinical facility first administers the ADOS examination and then scores the individual based on his or her observations to determine the final diagnosis. The initial assessment can take between 30 and 60 minutes, and the scoring increases the total time to between 60 and 90 minutes. Due to variance in inter-rater reliability, additional professionals may re-score the individual, further increasing the time between testing and receipt of the official clinical diagnosis.⁴ Even ignoring the geographic and logistical hurdles in finding a certified professional to administer the ADOS, the time required for the exam and the rise in the number of children at risk for ASD have contributed to increasing bottlenecks in the healthcare system.⁵ The average age of diagnosis in the United States hovers stubbornly around 4 years,⁵ and families may wait as long as 13 months for the diagnosis after the initial screening,⁶ and even longer if they are from a minority population or are of lower socioeconomic status.⁷ Such delays impede early intervention speech and behavioral therapies that provide substantial benefits to children.^{8, 9} For the estimated 27% of individuals undiagnosed at 8 years of age,⁵ opportunities for therapeutic intervention have dissipated. Therefore, risk assessment and triage tools that can reach families earlier and enable them to receive the care they need are badly needed. Given the promising findings from our previous work on the first module of the ADOS^{10, 11} and the ADI-R¹² we postulated that we might obtain similar results when examining records from the other two modules of the ADOS, which apply to a large portion of the population suspected of having an ASD.¹³ Improving upon our previous work, here we utilized the best-estimate clinical diagnosis when possible and incorporated stepwise backward feature selection into our machine learning pipeline to quantitatively select the optimal set of significant behavioral features that can accurately detect ASD risk in a large population of individuals.

We assembled a collection of ADOS evaluations for 4540 individuals and developed a classifier for each module that exhibited optimal performance in classification of individuals both on and off the spectrum. Each classifier was trained on over 600 individuals and tested independently on more than 1000 individuals. The resulting classifiers contained fewer items than the ADOS-2 (ref. 14) and pinpointed several behaviors that could help guide future efforts focused on expedited observation-based screening both in and out of clinical settings. Data for modules 2 and 3 came from five separate repositories: Boston Autism Consortium (AC), Simons Simplex Collection v14 (SSC),¹⁵ Autism Genetic Research Exchange (AGRE),¹⁶ National Database of Autism Research (NDAR),¹⁷ and the Simons Variation in Individuals Project (SVIP).¹⁸ (Table 1). The ADOS examination classified individuals into three discrete categories (autism, autism spectrum, and non-spectrum) by summing the scores from a subset of items from the ADOS and cross-referencing this total score with the thresholds for autism, autism spectrum and non-spectrum.

ADOS scores for each item fall on an integer scale of 0–3, with scores of 7 or 8 reserved for behaviors not exhibited during the test. In a preprocessing step, the ADOS algorithm recodes scores of 3 to 2 and scores of 7 or 8 to 0 to improve reliability and validity.¹⁴ For our analyses, we recoded scores of 7 and 8 as 0, but elected to leave scores of 2 and 3 distinct answer codes to increase granularity in the classification. In addition, we grouped strict autism and autism spectrum categories together into one autism spectrum cohort, leaving only two classes for machine learning, an autism spectrum class and a non-spectrum class. Table 1 Training and testing data description Recruitment varied by study. Individuals in AC, AGRE,NDAR and SSC were recruited with a suspicion of having ASD, and individuals in the SVIP were required to have or be related to an individual with the 16p11.2 duplication/deletion.¹⁹ Gender remained consistent across both modules; males comprised 82–86% of individuals with ASD and 61–63% of individuals without ASD. The intelligence quotient (IQ) was consistent across both modules and between individuals with and without ASD (Table 2). Due to the diverse phenotypic effects of the 16p11.2 duplication/deletion, individuals in SVIP were enriched for comorbidities, including ADHD, developmental coordination disorder, phonological disorder and others. Thus, the individuals in the SVIP proved useful for testing the specificity of the algorithms (i.e., differentiating between ASD and other behavioral disorders and developmental delays). A complete description of the phenotypic diversity of the samples used is provided in Supplementary Table S1. Different versions of the ADOS were used in each data set, namely ADOS Version 1 (ref. 4) (AC, SSC, AGRE andNDAR), and ADOS version 2 (ref. 14) (SVIP).

To ensure consistency across data sets, we computed the ADOS-2 diagnosis for all individuals in AC, AGRE,NDAR and SSC using the ADOS-2 algorithms. We elected to do this because the ADOS-2 incorporates repetitive and restrictive behaviors, and it has been shown to more accurately identify cases from non-spectrum controls in lower-functioning populations.¹⁴ Not all individuals had either a clinician's diagnosis or the best-estimate clinical diagnosis. Specifically, 76% of the ASD cases and 46% of the non-autism controls had a recorded clinician's diagnosis or the best-estimate clinical diagnosis. Therefore, we elected to use the diagnosis provided by the ADOS-2 algorithm for our classifier labels in the training processes. Table 2 Sample description Machine learning We used machine learning to develop two classifiers: one derived from ADOS module 2 and the other from ADOS module 3. For each module, our strategy involved training eight different machine learning algorithms (Table 3) using stepwise backward feature selection, and testing the final classifier on four independent data sets. We chose stepwise backward feature selection over stepwise forward feature selection to allow for interactions between features.²⁰ We used each module's items as features, and the individuals' ADOS-2 diagnoses as our prediction class. All machine learning analyses were performed in R and Weka21 (version 3.7-9). As the number of individuals with ASD outnumbered those without in both module 2 (4–1) and module 3 (5–1) across all data sets, we selected the data sets with the highest number of individuals without ASD as our training set. Module 2 classifiers were trained from anNDAR collection of 362 with ASD and 282 individuals without ASD. Module 3 classifiers were trained on AGRE, with 510 individuals with ASD and 93 individuals without ASD (Table 1). Table 3 Machine learning algorithms used in training The 28 features for each of module 2 and module 3 were ranked using a support vector machine (SVM) based on their ability to differentiate between individuals with and without ASD. We used stepwise backward feature selection with 10-fold cross-validation in all eight machine learning algorithms. This feature selection procedure determined the optimal number of features by first training a classifier with all 28 features, iteratively removing the lowest-ranked feature, and building a new model using 90% of the data for training and the remaining 10% for testing. [cour de mathématique Seme.pdf](#)



The process ended once a single feature remained, yielding a final set of 28 classifiers, which could each be assessed for their sensitivity and specificity. By plotting the sensitivity, specificity and accuracy of each classifier versus the number of features, the best classifier was identified as the one with the highest performance and smallest number of features (Figure 1). We aimed to maximize specificity (the true negative rate) over sensitivity (the true positive rate) because of the large class imbalance (Table 1). Figure 1 Module 2 logistic regression and logistic model tree (LMT) training results. Sensitivity and specificity of the module 2 logistic regression and LMT classifiers based on the number of features used during training on the National Database of Autism Research are provided in Table 1. The nine-feature logistic regression classifier (blue dot) was used in testing Validation After finding the optimal classifiers for modules 2 and 3, we validated these classifiers on the remaining four data sets not used for training. The module 2 classifier was tested on AC, AGRE, SSC and SVIP, totaling 1089 individuals with ASD and 66 individuals without ASD (Table 1). The module 3 classifier was tested on AC,NDAR, SSC and SVIP, totaling 1924 individuals with ASD and 314 individuals without ASD (Table 1). Two algorithms using the same nine features displayed optimal performance on theNDAR training data (98.90% sensitivity, 99.58% specificity and 98.76% accuracy), a logistic regression²² and a logistic model tree (LMT)²³ (Table 3; Figure 1). [atomic habits worksheets](#) LMTs combine decision trees with logistic regression, thereby allowing the incorporation of nonlinear patterns into the model. When such nonlinear patterns exist and help explain additional variance in the data, LMTs outperform logistic regression.²³ However, in our data, no such patterns were detected and the nine-feature LMT consisted of just the root node with a logistic regression model. Thus we chose logistic regression over LMT for use in further testing and validation. For independent validation of the nine-feature logistic regression classifier, we collated score sheets for module 2 from the AC, AGRE, SSC and SVIP (Table 1) to determine whether the classifier could recapitulate the sensitivity and specificity of training data on held-out test data.

How to Cite:
APA: Hu, V., & Lord, C. (2014). The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores. *Journal of autism and developmental disorders*, 44(8), 1996-202.

Harvard: Hu, V. & Lord, C. 2014. The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores. *Journal of autism and developmental disorders*, 44(8), pp.1996-202.

Considerations

Although we have provided this resource, to use freely at your discretion, we reiterate the request for accurate and honest qualitative descriptions of the observed behaviours, as recommended in the ADOS-2 manual.

"In communicating with other professionals (with family's consent), it is still recommended that the clinician report the raw and standardized severity scores from the ADOS-2 Classification, rather than rely on scores to communicate meaningful information about the child's diagnostic status. In general, raw and standardized severity scores are disseminated in a way that does not suggest that the specific scores may be more meaningful than disseminated in a way that does not suggest that the specific scores may be more meaningful than the overall total scores or the assigned ratings of algorithm scores (i.e., items, domain, and Overall Total scores) in clinical or research reports because the specific scores may be misleadingly disseminated in a way that may not be consistent with the overall classification. ADOS-2 Comprehension scores may only be reported with caution, as they have distinct 'pitfalls' in interpretation due to their narrow range (representing only a portion of the child's overall symptomatology) and the lack of evidence for the ADOS-2, the lack of epidemiological samples on which to calibrate scores, and the scarcity of research on the validity of the ADOS-2 Comprehension scores. Second Edition (ADOS-2; Lord, Risi, Risi, Gotham, & Guthrie, 2012; Lord, Risi, et al., 2012).

References:
Lord, C., Risi, K., Gotham, K. *Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) Manual (Part B): Toddler Module*. Torrance, CA: Western Psychological Services, 2012.
Lord, C., Risi, K., Gillberg, P.C., Risi, S., Gotham, K., Bishop, S. *Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) Manual (Part A): Modules 1-4*. Torrance, CA: Western Psychological Services, 2012.

Purpose of Revision

The Autism Diagnostic Observation Schedule, 2nd Edition manual includes revised diagnostic algorithms and standardized severity scores for modules used to assess children and adolescents of varying ages.

However, comparable revisions for Module 4 are not available in the ADOS-2 manual. Hu & Lord (2014) revised the Module 4 algorithm and calibrated raw overall and domain totals to provide revised ADOS-2 scores.

Sensitivity and specificity of the revised Module 4 algorithm exceeded 80% in the overall sample. Module 4 calibrated severity scores provide quantitative estimates of ASD symptom severity that are relatively independent of participant characteristics. The revised algorithm increases comparability of ADOS scores across modules.

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Across our four test sets, the logistic regression classifier misclassified 13 out of 1089 individuals with ASD (98.81% sensitivity) and 7 out of 66 individuals without ASD (89.39% specificity), resulting in 98.27% accuracy (Supplementary Table S2).

Administration section

Order and structure of the administration

Observation and administration guidelines

Coding section

Items listed by five subsections: Language and Communication; Reciprocal Social Interaction; Play; Stereotyped Behaviors and Restricted Interests; Other

Administrator's instructions

Examiner chooses one rating of the following: 0, 1, 2, 3, 4, 7, 8, 9 according to Coding Conventions described in the manual and specific descriptions in a particular item.

Algorithm form

Each Module contains one or two diagnostic algorithms:

Toddler Module Algorithms

• All younger/older with few to no words – for children with chronological age between 12 and 20 months OR children aged 21-30 months who used fewer than five words during an ADOS-2 assessment.

• Older with some words – for children with chronological age between 21 and 30 months who used at least five different words.

Module 1 Algorithms

Fewer than five words – for children who used fewer than five words during an ADOS-2 assessment.

Five or more words – for children who used at least five different words during an ADOS-2 assessment.

Younger than 5 years – for children with chronological age below 5 years 0 months.

5 years or older – for children with chronological age at least 5 years 0 months.

Module 2 Algorithms

For all participants assessed with Module 3.

For all participants assessed with Module 4.

Examiner converts item codes to algorithm scores:

• range of 1 to 8, 9 to algorithm scores of 0, 1, 2

• ratings of 1, 8, 9 to algorithm scores of 0, 1, 2

Examiner does not convert ratings of 0, 1, 2, 3, 4, 7, 8, 9 to algorithm scores of 0, 1, 2, 3, 4, 7, 8, 9 directly to the algorithm scores into two domains.

Social Affect (SA) and Restricted and Repetitive Behavior (RRB)

SA Total = SA Total + RRB Total
SA Total + RRB Total = Overall Total

Examiner covers the Overall Total for the ADOS-2 Classification (two cut-offs: for autism and lower for autism spectrum) and the ADOS-2 Companion Score (10-point severity metric).

Based on Lord et al. (2012a,b)

The 13 misclassified individuals with autism, 6 had a clinical diagnosis of autism, 3 had a clinical diagnosis of pervasive developmental disorder-not otherwise specified and 1 had a best-estimate clinical diagnosis of non-spectrum. For the seven misclassified individuals without autism, three had a non-spectrum clinical diagnosis, three had an autism best-estimate clinical diagnosis and one individual had a clinical diagnosis of broad spectrum. For a subset of individuals, their best-estimate clinical diagnosis was available (autism N=618, non-spectrum N=35). When independently predicting the best-estimate clinical diagnosis, the sensitivity and specificity of the nine-feature logistic regression model was 98.38% and 88.57%, respectively. Although the ADOS-2 module 2 uses different algorithms for individuals based on their age, our nine-feature logistic regression classifier does not. Because age and the log-odds of the prediction were significantly correlated ($r=0.45$; $P<2.2 \times 10^{-16}$), we hypothesized that adding age as a covariate to the regression might explain additional variance in the outcome. However, the effect of age on the classifier was negligible (0.015 , odds ratio 1.055), and adding it to the model slightly decreased sensitivity (-0.28%) and accuracy (-0.16%). Therefore, we elected not to incorporate age into the regression. IQ measures were also significantly correlated after controlling for gender, including full-scale IQ ($r=-0.37$; $P<2.2 \times 10^{-16}$), verbal IQ ($r=-0.42$; $P<2.2 \times 10^{-16}$) and nonverbal IQ ($r=-0.27$; $P<3.8 \times 10^{-15}$). The behaviors tested assessed by the module 2 classifier segregated into the two domains associated with ASD: (1) social communication and social interactions and (2) restricted interests and repetitive behaviors. Feature A5 (stereotyped/idiomatic use of words or phrases), A8 (descriptive, conventional, instrumental or informational gestures), B1 (unusual eye contact), B3 (shared enjoyment in interaction), B6 (spontaneous initiation of joint attention), B8 (quality of social overtures) and B10 (amount of reciprocal social communication) correspond to the domain of social communication and interaction. D2 (hand and finger and other complex mannerisms) and D4 (unusual repetitive interests or stereotyped behaviors) stem from the domain of restricted interests and repetitive behaviors. Feature A5 (stereotyped/idiomatic use of words or phrases), D1 (unusual sensory interest in play material/person), D2 (hand and finger and other complex mannerisms) and D4 (excessive interest in unusual or highly specific topics or objects) stem from the domain of restricted interests and repetitive behaviors. Despite significant evidence for the genetic heritability of ASD, it remains diagnosed through behavior. Although use of standard instruments for ASD diagnosis has been effective, the practice remains difficult to scale and time intensive, contributing to the growing waiting times between initial warning signs and diagnosis. *nautical almanac.pdf* Machine learning techniques have been previously applied by our group and others to test whether ADOS10, 11, 12 and ADHD26 detection can be achieved with smaller numbers of behavioral measurements. Here, we sought to expand upon our previous work to a wider range of ages and levels of vocabulary by applying machine learning techniques to record clinical evaluations of individuals using modules 2 and 3 of the ADOS. We implemented stepwise backward feature selection with eight machine learning algorithms to create small but robust classifiers that retained levels of sensitivity and specificity similar to those of the full ADOS. The logistic regression algorithm produced the top-performing classifier for module 2 using nine features that exhibited 98.81% sensitivity and 89.39% specificity when tested across 1089 individuals with ASD and 66 individuals without ASD. A SVM consisting of 12 behavioral items showed the optimal performance when run on score sheets from module 3, exhibiting 97.71% sensitivity and 97.20% specificity. Of the 44 individuals with ASD who were misclassified, clinical diagnoses were available for 30. Six had a confirmed autism diagnosis, six had Asperger's disorder and the remaining 18 had pervasive developmental disorder-not otherwise specified. For the six individuals without autism that were misclassified, three had a non-spectrum clinical diagnosis, and the remaining three individuals had no recorded clinical or best-estimate clinical diagnosis. For the individuals for whom a best-estimate clinical diagnosis was available (autism N=1568; non-spectrum N=175), the 12-feature SVM displayed 99.11% sensitivity and 90.86% specificity. (Figure 3) Figure 2Module 3 SVM training results. For the two classes: autism (red) and non-spectrum (blue). Forty-four misclassified individuals with autism (red triangles), and six individuals without autism (blue circles) contributed to 97.71% sensitivity and 97.20% specificity. ADOS, Autism Diagnostic Observation Schedule; SVM, support vector machine. Similar to the module 2 classifier, the features in the module 3 SVM classifier aligned with the two core domains of ASD. Feature A7 (reporting of events), A8 (conversation), A9 (descriptive, conventional, instrumental or informational gestures), B1 (unusual eye contact), B2 (facial expressions directed to others), B7 (quality of social overtures) and B9 (amount of reciprocal social interaction) correspond to the domain of social communication and interaction. A4 (stereotyped/idiomatic use of words or phrases), D1 (unusual sensory interest in play material/person), D2 (hand and finger and other complex mannerisms) and D4 (excessive interest in unusual or highly specific topics or objects) stem from the domain of restricted interests and repetitive behaviors. Despite significant evidence for the genetic heritability of ASD, it remains diagnosed through behavior. 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Although use of standard instruments for ASD diagnosis has been effective, the practice remains difficult to scale and time intensive, contributing to the growing waiting times between initial warning signs and diagnosis. *nautical almanac.pdf* Machine learning techniques have been previously applied by our group and others to test whether ADOS10, 11, 12 and ADHD26 detection can be achieved with smaller numbers of behavioral measurements. Here, we sought to expand upon our previous work to a wider range of ages and levels of vocabulary by applying machine learning techniques to record clinical evaluations of individuals using modules 2 and 3 of the ADOS. We implemented stepwise backward feature selection with eight machine learning algorithms to create small but robust classifiers that retained levels of sensitivity and specificity similar to those of the full ADOS. The logistic regression algorithm produced the top-performing classifier for module 2 using nine features that exhibited 98.81% sensitivity and 89.39% specificity when tested across 1089 individuals with ASD and 66 individuals without ASD. A SVM consisting of 12 behavioral items showed the optimal performance when run on score sheets from module 3, exhibiting 97.71% sensitivity and 97.20% specificity. Of the 44 individuals with ASD who were misclassified, clinical diagnoses were available for 30. Six had a confirmed autism diagnosis, six had Asperger's disorder and the remaining 18 had pervasive developmental disorder-not otherwise specified. For the six individuals without autism that were misclassified, three had a non-spectrum clinical diagnosis, and the remaining three individuals had no recorded clinical or best-estimate clinical diagnosis. 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