

# Computer-Aided Recognition of Facial Attributes for Fetal Alcohol Spectrum Disorders

Matthew Valentine, MD,<sup>a</sup> Dustin C.J. Bihm, MS,<sup>a</sup> Lior Wolf, PhD,<sup>b</sup> H. Eugene Hoyme, MD,<sup>c,d</sup> Philip A. May, PhD,<sup>e,f</sup> David Buckley, MA,<sup>f</sup> Wendy Kalberg, MA, LED,<sup>f</sup> Omar A. Abdul-Rahman, MD<sup>g</sup>

abstract

**OBJECTIVES:** To compare the detection of facial attributes by computer-based facial recognition software of 2-D images against standard, manual examination in fetal alcohol spectrum disorders (FASD).

**METHODS:** Participants were gathered from the Fetal Alcohol Syndrome Epidemiology Research database. Standard frontal and oblique photographs of children were obtained during a manual, in-person dysmorphology assessment. Images were submitted for facial analysis conducted by the facial dysmorphology novel analysis technology (an automated system), which assesses ratios of measurements between various facial landmarks to determine the presence of dysmorphic features. Manual blinded dysmorphology assessments were compared with those obtained via the computer-aided system.

**RESULTS:** Areas under the curve values for individual receiver-operating characteristic curves revealed the computer-aided system ( $0.88 \pm 0.02$ ) to be comparable to the manual method ( $0.86 \pm 0.03$ ) in detecting patients with FASD. Interestingly, cases of alcohol-related neurodevelopmental disorder (ARND) were identified more efficiently by the computer-aided system ( $0.84 \pm 0.07$ ) in comparison to the manual method ( $0.74 \pm 0.04$ ). A facial gestalt analysis of patients with ARND also identified more generalized facial findings compared to the cardinal facial features seen in more severe forms of FASD.

**CONCLUSIONS:** We found there was an increased diagnostic accuracy for ARND via our computer-aided method. As this category has been historically difficult to diagnose, we believe our experiment demonstrates that facial dysmorphology novel analysis technology can potentially improve ARND diagnosis by introducing a standardized metric for recognizing FASD-associated facial anomalies. Earlier recognition of these patients will lead to earlier intervention with improved patient outcomes.



<sup>a</sup>Department of Pediatrics, University of Mississippi Medical Center, Jackson, Mississippi; <sup>b</sup>FDNA Inc, Boston, Massachusetts; <sup>c</sup>Sanford Research and School of Medicine, University of South Dakota Sanford, Sioux Falls, South Dakota; <sup>d</sup>Center for Applied Genetics and Genomic Medicine and Department of Pediatrics, College of Medicine, University of Arizona, Tucson, Arizona; <sup>e</sup>Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; <sup>f</sup>Center on Alcoholism, Substance Abuse, and Addictions, The University of New Mexico, Albuquerque, New Mexico; and <sup>g</sup>Department of Genetic Medicine, Munroe-Meyer Institute for Genetics and Rehabilitation, University of Nebraska Medical Center, Omaha, Nebraska

Dr Abdul-Rahman conceptualized and designed the study; Mr Valentine drafted the initial manuscript and completed the first revision of the manuscript; Mr Bihm drafted the second and third revision of the manuscript to produce the final form as submitted; Dr Wolf conducted facial and statistical analyses and contributed to revision of the manuscript as submitted; Dr Hoyme served as the lead expert dysmorphologist and contributed to revision of the manuscript as submitted; Dr May served as the principal investigator for the Fetal Alcohol Syndrome Epidemiology Research study that initially collected the data used for this study and he critically

**WHAT'S KNOWN ON THIS SUBJECT:** Alcohol-related neurodevelopmental disorder, a category within fetal alcohol spectrum disorders, represents a diagnostic challenge as it lacks apparent morphologic clues to diagnosis. Earlier detection and intervention facilitates improved patient outcomes in fetal alcohol spectrum disorders.

**WHAT THIS STUDY ADDS:** We report improved efficiency in the detection of patients with alcohol-related neurodevelopmental disorder by using computer-aided methods in comparison with standard, manual methods.

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Fetal alcohol spectrum disorders (FASDs) represent an array of structural anomalies and neurocognitive disabilities caused by prenatal alcohol exposure. The harmful nature of prenatal exposure to ethanol is well known, and many mechanisms of teratogenicity have been proposed. Craniofacial development is intimately linked with brain induction and expansion, which explains the association between FASD and certain facial anomalies.<sup>1</sup> Ethanol affects the developing fetus via a diverse range of mechanisms. Importantly, the teratogenic effects of ethanol affect the developing fetus in a temporally dependent manner. Because of this, phenotypic differences in disorders that fall under the FASD umbrella may be evident, even with subtle differences in the stage of prenatal alcohol exposure.<sup>2-5</sup>

FASD as an entity represents a considerable financial and clinical burden worsened by the fact that many affected individuals go undetected until school age. Late recognition of the etiology for neurocognitive deficits associated with this clinical spectrum leads to poorer developmental outcomes in affected individuals. In addition to primary disabilities, such as decreased cognitive and executive function, adolescents and adults with FASD also face a high rate of secondary disabilities such as problems at school, trouble with the law, alcohol abuse, and mental illness.<sup>6</sup> In examining risk factors for adverse life outcomes in FASD, 1 of the strongest correlates of adverse life outcomes, such as disrupted school experiences, is lack of an early diagnosis, with greater delay in diagnosis yielding greater odds of adverse outcomes.<sup>7</sup> Consequently, early recognition and diagnosis of FASD should be prioritized by health care professionals aiming to provide adequate support to these patients

and minimize the economic impact of the disease.

The range of FASD includes the following diagnostic categories: (1) fetal alcohol syndrome (FAS), (2) partial fetal alcohol syndrome (PFAS), (3) alcohol-related birth defects (ARBDs), and (4) alcohol-related neurodevelopmental disorders (ARNDs).<sup>8</sup> Although there are clear diagnostic criteria for FAS, PFAS, and ARBD, a major challenge remains in the effective recognition of patients with ARND because of the relative paucity of specific, easily identifiable features. Although FAS and PFAS can be diagnosed by using physical findings (small head circumference, short palpebral fissures, smooth philtrum, thin vermilion border of the upper lip, and growth deficiency) and neuropsychological evaluation without documented alcohol exposure, ARND diagnostic criteria require documented alcohol exposure because of the lack of physical findings.<sup>8</sup> In addition to confirmed maternal alcohol exposure, the diagnostic criteria for ARND that is currently available require recognition of a complex pattern of cognitive and/or behavioral abnormalities inconsistent with developmental level that cannot be explained by genetic predisposition, family background, or environment alone.<sup>8-11</sup> As obvious dysmorphic features can be lacking in cases of ARND that do not meet the first criterion, there have been several attempts to accurately define the neurocognitive profile of patients with ARND. The complex nature of defining this neurocognitive profile, however, is demonstrated by the need for advanced cognitive tests involving higher-level processing because IQ tests may be inadequate to differentiate children with ARND from those with developmental disabilities resulting from other causes.<sup>9</sup> Despite some success in profiling ARND neurocognitive

characteristics, challenges remain in finding a simple and effective tool that can be deployed in the clinical setting to aid in the diagnosis of ARND.

Although the craniofacial clinical criteria for ARND have historically only included reduced head circumference, it has been noted that ARND patients have an increase in minor facial anomalies compared with controls but fewer than those observed in cases of FAS or PFAS.<sup>12,13</sup> This suggests there may be some structural findings on physical examination that could be used to aid in the diagnosis of ARND. Evidence exists that computer-based analysis of facial images can detect subclinical features in patients with ARND.<sup>14</sup> However, the technology used required complex systems involving three-dimensional cameras that may be impractical in the clinical setting. Therefore, we examined the ability of a commercially available, computer-based facial dysmorphology analysis tool that uses two-dimensional images taken with a standard “point-and-click” camera to aid in the diagnosis of FASD and, specifically, to determine if subclinical facial features in ARND can be detected.

## METHODS

Protocols and consent forms were approved by the Human Research Review Committee of the University of New Mexico School of Medicine. Separate active consents for children and mothers to participate were obtained.

Participants in this study were gathered from the Fetal Alcohol Syndrome Epidemiology Research (FASER) database. In FASER studies, children aged 5 to 9 years were evaluated for FASD from locations in South Africa, Italy, and the United States.<sup>15-18</sup> The collection of patients in the FASER database relied on active case ascertainment methods to facilitate the efficient identification

of children across the full continuum of FASD diagnoses. The initial sample selection and screening for cases and controls considered deficiencies in growth parameters ( $\leq 10$ th or 25th percentile using height, weight, and head circumference measures) and also random selection of children from the same schools to ensure the representativeness of the sample for the particular population. Subsequently, dysmorphology assessments of all sample children were performed.<sup>10</sup> Standard frontal and oblique photographs were taken of all children. Each child was examined in a blinded manner and independently by 2 dysmorphologists without information about potential prenatal alcohol exposure; affected children were later classified into the appropriate diagnostic category after maternal interviews and neuropsychological testing were conducted in a structured multidisciplinary case conference as previously described.<sup>11</sup> The collected data set of images comprised frontal and oblique photographs of a random subset of patients with FASD from the FASER database: FAS ( $n = 36$ ), PFAS ( $n = 31$ ), ARND ( $n = 22$ ). Sample sizes represent all available cases of FASD ( $N = 89$ ) present in the FASER database that matched the selection criteria at the time of this study. These were compared with a cohort of control children who were randomly selected and determined to not be affected with FASD and who displayed normal morphology, growth, and development ( $N = 50$ ).

Appropriate categorical diagnoses were assigned based on specific criteria. A diagnosis of FAS required the following: (1) at least 2 of 3 cardinal facial features (ie, short palpebral fissures, thin vermilion border, smooth philtrum), (2) growth restriction (prenatal and/or postnatal), and (3) evidence of deficient brain growth (presumed by structural brain abnormality and/or occipitofrontal head circumference

[OFC]  $\leq 10$ th percentile). The requirements for a diagnosis of PFAS included the following: (1) at least 2 of 3 cardinal facial features, and (2) prenatal and/or postnatal growth restriction, (3) OFC  $\leq 10$ th percentile, or (4) a complex behavioral pattern or cognitive abnormalities inconsistent with developmental level. Regarding the cognitive abnormalities, it was required that the observed abnormalities could not be explained by genetic composition (eg, aneuploidies, etc), family history, or environment alone.<sup>15,18</sup> A preliminary ARND diagnosis required observance of OFC  $\leq 10$ th percentile or specific behavioral or cognitive abnormalities. Thorough maternal interviews were conducted to confirm maternal alcohol consumption during pregnancy. Confirmed maternal alcohol consumption during pregnancy was required for a diagnosis of ARND. This was in contrast to the diagnosis of cases of FAS and PFAS in which confirmation of maternal alcohol consumption was not strictly required for diagnosis. No cases of ARBD were observed in the cohort.

### The Dysmorphology Scoring System

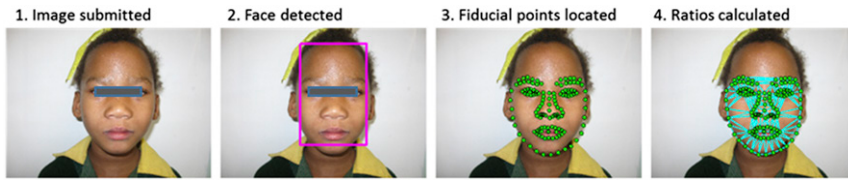
The Dysmorphology Scoring System (DSS) was initially published in 2005 as a research tool by which the dysmorphic features associated with FASD could be quantified in an individual child, thus enabling comparison of overall dysmorphology among affected children.<sup>10</sup> However, the concept was originally envisioned by Dr Jon Aase at the University of New Mexico based on his experience in diagnosing FAS among the general population and Native American populations of New Mexico, Alaska, and other parts of the western United States. The DSS uses a point system from 0 to 3 based on the degree of specificity that a feature has to an FASD diagnosis. For example, each of the 3 cardinal facial features is given a score of 3,

whereas “hockey stick” creases and clinodactyly are given a score of 1.

### Automated Face Analysis

Automated face analysis was conducted by using the facial dysmorphology novel analysis (FDNA) technology, used in a proprietary software tool called Face2Gene (FDNA Inc, Boston, MA). This technology combines several methodologies of facial recognition from photographs to generate accurate information despite individual differences in variables such as ethnicity, sex, and age.<sup>19</sup> Additionally, this combined methodology maintains superior performance even in the event of skewed image characteristics such as illumination, pose, and expression. The image analysis pathways are demonstrated in Fig 1. First, a subject’s face is detected within the image with a statistical face detector, and the background is discarded. Multiple anatomic points are then located on the face (eg, corners of the eyes and nose, etc). Next, a description of the face under investigation is conducted as multiple lengths, angles, and ratios are computed for each face. These values are then used in combination with statistical mechanisms analyzed statistically to evaluate for the presence of dysmorphic features. Interestingly, because the software analyzes a two-dimensional image, it can make an accurate diagnosis by analyzing the ratios and proportions of the face rather than relying on the features pediatricians most commonly evaluate. The areas that are identified as discriminators include the philtrum and palpebral fissures, although there are other areas that are also recognized as being altered.

In addition to the identification of individual features, we applied a gestalt descriptor to capture and visualize the overall appearance of each face. Because this gestalt



**FIGURE 1**  
Demonstration of FDNA technology.

system considers the entire face, it was helpful in reviewing the general appearance of faces of the patients with FASD. The gestalt system encodes the detected face as a compilation of measurements, with each describing the appearance at a specific point of the face. These measurements collectively form a robust template of the face that can be readily compared to other faces.<sup>19</sup> This deep phenotyping technology has also been described as having a role in objectively making diagnoses after a whole-exome analysis.<sup>20</sup>

### Experimental Protocol

We compared the rate of discrimination achieved by 2 methods: (1) a manual score guided by the DSS with its comprehensive list of manually annotated features and (2) a computer-aided score using the FDNA technology. Four experiments were conducted. In the first 3 experiments, patients with FAS, PFAS, and ARND were considered, and the efficiency of recognition of each specific disorder was evaluated. In the fourth experiment, the 3 groups of disorders were united as a single group before attempting discrimination. In all 4 experiments, the same group of 50 controls was used.

For the second method (FDNA technology), which relies on automatic detections, the list of DSS features used was divided into 2 groups: those detectable in facial images and those that are nonfacial. The nonfacial features were taken from the score sheets completed by experienced pediatric dysmorphologists and used alongside

a set of 76 frontal and 39 lateral facial features that were automatically detected. The system then combined the 2 feature types together using a linear classifier whose coefficients were obtained from a separate set of training images put aside for this purpose in a cross-validation manner (see below). The distinction between the 2 groups of features is natural in the clinical setting because most clinicians would not experience difficulty in identifying the nonfacial features; yet challenges in the detection of the facial features can be extensive and often require expertise in dysmorphology.

To estimate the statistical power of the 2 methods to discriminate between patients with FASD and control patients, a cross-validation scheme was used. As with other such schemes, the data were split randomly (multiple times) into training and test sets. Individuals used for training were excluded from the corresponding test set. In our experiments, each such set (train or test) contained half of the examples (both FASD and controls), and the random process was repeated 10 times. At each of the 10 rounds, the parameters of the automatic recognition methods were independently optimized on the training set and evaluated on the test set.

The receiver operating characteristic (ROC) curve is a widely accepted form of measuring classification success. Results for our experiment are reported by computing the area under the curve (AUC) statistic of the ROC curve. An AUC of 1 is indicative of perfect accuracy whereas an AUC

of 0.5 is the equivalent performance obtained by a completely random coin-flipping system.

### RESULTS

The area under the ROC curve for the 4 experiments as well as sensitivity, specificity, and positive and negative predictive values are listed in Table 1. Permutation tests were run on each of the 4 tests (10 000 random tests each) to estimate the probability of obtaining these results in a random manner. To this end, the labels are randomly permuted over the same descriptors 10 000 times, for each of the tests. Thus, the resulting *P* value shown in Table 2 is the probability of the obtained result over the distribution of random permutations. Individual ROC curves are shown in Fig 2. AUC values for these curves indicated that the semiautomatic method for detecting FASD patients was able to achieve an overall performance comparable to the manual system. Of particular interest, we found cases of ARND to be identified more efficiently by the semiautomatic system than by the manual method.

Visualization of the gestalt analysis is shown in Fig 3. Facial regions colored red represent the primary areas identified in support of an FAS classification, whereas regions less supportive of such a diagnosis are marked with cooler colors. The gestalt analyses were found to be helpful in drawing attention to the most relevant facial regions that support an FASD. In Fig 4, we illustrate gestalt analyses that compare ARND to FAS and PFAS. The average response on patients with ARND is shown for 3 gestalt detectors: ARND, FAS, and PFAS. On visualization, faces of typical patients with ARND appeared to pick up a more diffuse pattern of subtle facial cues in support of classification as ARND. In contrast, FAS and PFAS detectors appeared to focus detection



**TABLE 1** AUC Values Obtained by Manual and Computer-Aided Methods for 4 Experiments

	Manual Score				Computer-Aided Score						
	AUC ± SD (95% CI)	Sensitivity ± SD (95% CI)	Specificity ± SD (95% CI)	Positive Predictive Value ± SD (95% CI)	Negative Predictive Value ± SD (95% CI)	Positive Likelihood Ratio	Negative Likelihood Ratio	Positive Likelihood Ratio	Negative Likelihood Ratio		
FAS versus control	0.96 ± 0.03 (0.9414–0.9786)	0.99 ± 0.03 (0.9710–1.0000)	0.89 ± 0.14 (0.8031–0.9769)	0.87 ± 0.04 (0.8442–0.8958)	0.99 ± 0.12 (0.9138–1.0000)	9.14	0.02	0.95 ± 0.02 (0.9376–0.9624)	0.88 ± 0.04 (0.8566–0.9034)	9.33	0.25
PFAS versus control	0.89 ± 0.02 (0.8776–0.9024)	0.76 ± 0.16 (0.6621–0.8579)	0.89 ± 0.12 (0.8138–0.9662)	0.81 ± 0.08 (0.7597–0.8603)	0.86 ± 0.06 (0.8210–0.8990)	7.03	0.27	0.82 ± 0.06 (0.7828–0.8572)	0.67 ± 0.07 (0.6259–0.7141)	3.52	0.27
ARND versus control	0.74 ± 0.04 (0.7152–0.7648)	0.43 ± 0.24 (0.2789–0.5811)	0.92 ± 0.16 (0.8218–1.0000)	0.7 ± 0.08 (0.6490–0.7510)	0.79 ± 0.10 (0.7251–0.8549)	5.51	0.62	0.84 ± 0.07 (0.7966–0.8834)	0.7 ± 0.13 (0.6157–0.7843)	6.0	0.55
Any FASD versus control	0.88 ± 0.02 (0.8676–0.8924)	0.87 ± 0.03 (0.8530–0.8870)	0.77 ± 0.10 (0.7050–0.8350)	0.87 ± 0.03 (0.8470–0.8930)	0.77 ± 0.07 (0.7256–0.8144)	3.87	0.17	0.86 ± 0.03 (0.8414–0.8786)	0.83 ± 0.03 (0.8143–0.8457)	2.88	0.16

CI, confidence interval.

**TABLE 2** Results of Permutation Tests Showing P Values for Each of the 4 Tests

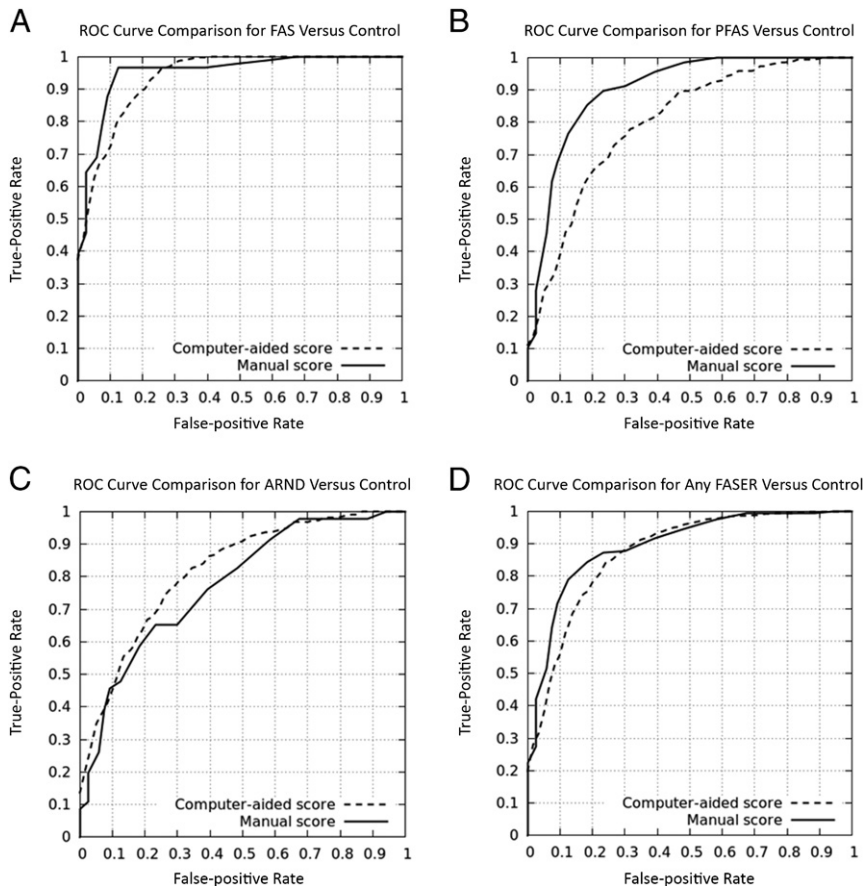
	Permutation Test P Value
FAS versus control	.0009
PFAS versus control	.0117
ARND versus control	.0057
Any FASD versus control	.0012

cues on a narrower spectrum of specific facial characteristics and regions. These findings indicate the ARND phenotype is not simply a mild FAS or PFAS phenotype; instead, these analyses support ARND as an independent, identifiable structural phenotype.

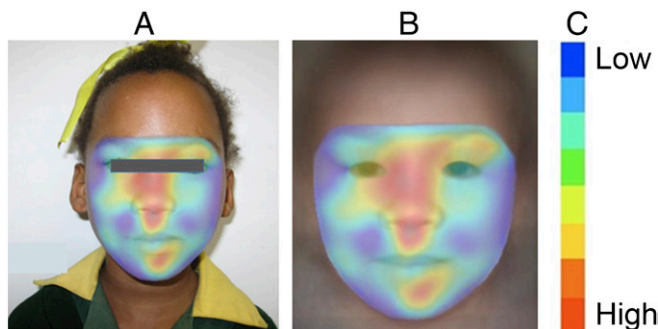
## DISCUSSION

FASDs represent a significant disease burden among the pediatric population. FASD encompasses the diagnoses of FAS, PFAS, ARBD, and ARND. Often under- or misdiagnosed,<sup>21</sup> this spectrum of disorders presents a variety of challenges in diagnosis as well as management of associated psychological and neurocognitive deficits. ARND represents a unique challenge in diagnosis because, to date, a unique ARND facial phenotype has not been formulated as opposed to the better-recognized dysmorphic facial phenotype of individuals with FAS and PFAS.<sup>14</sup> The diagnosis of ARND has historically required the expertise of trained dysmorphologists in addition to neuropsychological testing conducted by trained experts. Even with the aid of these specialists, diagnosis of ARND remains difficult, and there is a clear need for improved efficiency in diagnosing this disorder. We present our experiment as evidence that facial recognition technology can help clinicians improve the accuracy of diagnosing FASD, particularly ARND.<sup>14</sup>

In searching for improvement in diagnosis of FASD, we used the FDNA technology through the commercially



**FIGURE 2** ROC curves obtained for the 4 recognition experiments. Each plot compares the performance of a manual score based on DSS (solid) to a computer-aided one (hatched). A, FAS. B, PFAS. C, ARND. D, Any FASD.



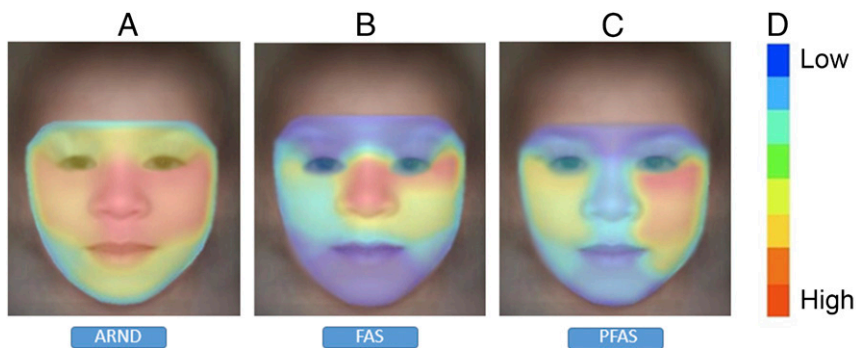
**FIGURE 3** A, The FAS heatmap overlaid on the input image. B, The same heatmap overlaid on a typical FAS face. C, Heatmap index. A facial region most supportive of the FAS classification is marked in red, while regions that are less supportive are marked with cooler colors.

available facial recognition and analysis software called Face2Gene and compared efficiency in diagnosis of cases of FASD conducted by this software to a manual method. Our findings revealed that the FDNA

technology, when applied to facial assessments, is nearly as accurate as the diagnosis of cases of FAS and PFAS by expert dysmorphologists. Additionally, with our results, we indicate the FDNA technology may

actually be more efficient than human dysmorphologists in the assessment and diagnosis of ARND. We describe evidence in support of the idea that subtle facial features exist in patients with ARND who are below the threshold of detection by dysmorphologists. As suggested by Fig 4, the diffuse pattern of structural anomalies detected by FDNA is less discrete for ARBD than for FAS or PFAS; however, general pediatricians, residents, nurses, and other trainees may have difficulty recognizing even the general features of FASD. In cases when prenatal alcohol exposure is documented or suspected, these clinicians can simultaneously improve their ability to categorize dysmorphological features of FASD and use the facial recognition software to screen for children who may need in depth psychological testing for ARND.

This improved detection of patients with ARND by the FDNA system is promising because ARND has been traditionally difficult to diagnose, especially by general pediatric clinicians. Furthermore, the FDNA system relies on two-dimensional image analysis rather than three-dimensional scans. This makes the technology accessible to clinicians because special capturing equipment is unnecessary. This could prove to be particularly important in developing nations where access to molecular testing is limited.<sup>22</sup> Although promising as a detection system, clinical assessment must be used adjunctively with FDNA when characterizing other domains within FASD diagnostic criteria. For example, clinical judgment is needed when assessing the significance of neurodevelopmental delays, the veracity of alcohol exposure reports, and in ruling out other possible genetic or teratogenic causes of the phenotypes identified. We believe further studies examining the diagnosis of ARND using the FDNA technology will provide additional



**FIGURE 4**  
Heatmap comparison of FASD showing all regions of the face provide cues supporting ARND classification; in FAS and PFAS, only few regions that correspond to the cardinal facial features support the diagnosis of FASD. The images show regions supporting classification of A, ARND; B, FAS; and C, PFAS. D, Correlation scale.

proof that facial recognition software can improve the accuracy and speed of ARND diagnosis.

If corroborated, our experiments imply that the FDNA technology could play a prominent role in FASD evaluation and provide an accessible tool for clinicians, especially general pediatricians who lack expertise in dysmorphology. The emergence of FDNA as a commercially available software application gives this technology the potential to prove itself as a useful application in the clinician’s toolbox because barriers to accessing this technology remain low for physicians.

### CONCLUSIONS

We found increased diagnostic accuracy for ARND via our computer-aided method. Because this category has been historically difficult to diagnose, we believe our experiment demonstrates that technology can improve ARND diagnosis by introducing a standardized metric for recognizing FASD associated facial anomalies. Further improvement in these methods will facilitate earlier recognition of these patients and, ultimately, lead to earlier intervention with improved patient outcomes in a number of areas, including academic, social, and psychological functioning.

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### ABBREVIATIONS

- ARBD: alcohol-related birth defect
- ARND: alcohol-related neurodevelopmental disorder
- AUC: area under the curve
- DSS: Dysmorphology Scoring System
- FAS: fetal alcohol syndrome
- FASD: fetal alcohol spectrum disorder
- FASER: Fetal Alcohol Syndrome Epidemiology Research
- FDNA: facial dysmorphology novel analysis
- OFC: occipitofrontal head circumference
- PFAS: partial fetal alcohol syndrome
- ROC: receiver operating characteristic

reviewed the manuscript; Mr Buckley supervised data entry and data transfer of images and data files for the study; Ms Kalberg supervised data collection and participated in the design of the study; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Omar A. Abdul-Rahman, MD, Department of Genetic Medicine, Munroe-Meyer Institute, University of Nebraska Medical Center, 985440 Nebraska Medical Center, Omaha, NE 68198-5440. E-mail: [omar.abdulrahman@unmc.edu](mailto:omar.abdulrahman@unmc.edu)

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