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DE NOVO CLASSIFICATION REQUEST FOR
COGNOA ASD DIAGNOSIS AID

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REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Pediatric Autism Spectrum Disorder diagnosis aid**. A pediatric Autism Spectrum Disorder diagnosis aid is a prescription device that is intended for use as an aid in the diagnosis of Autism Spectrum Disorder in pediatric patients.
>
> **NEW REGULATION NUMBER:** 21 CFR 882.1491
>
> **CLASSIFICATION:** Class II
>
> **PRODUCT CODE:** QPF

BACKGROUND

> **DEVICE NAME:** Cognoa ASD Diagnosis Aid
>
> **SUBMISSION NUMBER:** DEN200069
>
> **DATE DE NOVO RECEIVED:** November 3, 2020
>
> **SPONSOR INFORMATION:**
>
> Cognoa, Inc.
> 2185 Park Blvd.
> Palo Alto, California 94306

INDICATIONS FOR USE

The Cognoa ASD Diagnosis Aid is intended for use by healthcare providers as an aid in the diagnosis of Autism Spectrum Disorder (ASD) for patients ages 18 months through 72 months who are at risk for developmental delay based on concerns of a parent, caregiver, or healthcare provider.

The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process.

LIMITATIONS

The sale, distribution, and use of the device are restricted to prescription use in accordance with 21 CFR 801.109.

The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process.

The device is intended for use in conjunction with patient history, clinical observations, and other clinical evidence the healthcare provider determines are necessary before making clinical decisions. For instance, additional standardized testing may be sought to confirm the device output, especially when the device result is not Positive or Negative for ASD.

The device may give unreliable results if used in patients with other conditions that would have excluded them from the clinical study. Among those conditions are the following:
- Suspected auditory or visual hallucinations or with prior diagnosis of childhood onset schizophrenia.
- Known deafness or blindness.
- Known physical impairment affecting their ability to use their hands.
- Major dysmorphic features or prenatal exposure to teratogens such as fetal alcohol syndrome.
- History or diagnosis of genetic conditions (such as Rett's syndrome or fragile X).
- Microcephaly.
- History or prior diagnosis of epilepsy or seizures.
- History of or suspected neglect.
- History of brain defect injury or insult requiring interventions such as surgery or chronic medication.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Cognoa ASD Diagnosis Aid is a software as a medical device (SaMD) that utilizes a machine-learning algorithm that receives independent information from caregivers or parents, trained analysts, and healthcare professionals (HCPs) to aid in the diagnosis of ASD. It consists of multiple software applications and hardware platforms. Input data is acquired via a Mobile App, a Video Analyst Portal, and a HCP Portal.

- **Mobile App**: User interface (UI) for the caregiver or parent to upload videos of the patient via Wi-Fi connection and answer questions about key developmental behaviors. Interfaces with Application Programming Interface (API) server for transmission and management of patient data. Compatible with both iOS (versions 12 and 13) and Android platforms (versions 9 and 10).

- **Video Analyst Portal**: UI for trained analysts to review uploaded patient videos remotely and answer questions about the patients' behaviors observed in the videos.

- **HCP Portal**: UI for the HCP to answer questions about key developmental behaviors for the patient's age group, view device output and access the interactive dashboard to view all patient results, patient videos, answers to questionnaires administered and device performance data. Compatible with computer operating systems macOS (Catalina or Mojave) and Windows 10, and browsers Safari (versions 12 or 13) and Chrome (versions 84 or 85).

Following analysis of the input data, the Cognoa ASD Diagnosis Aid machine-learning algorithm produces a single scalar value between (b) (4) and (b) (4) which is then compared to preset thresholds to determine the classification. If the value is greater than the upper threshold, then the device output is 'Positive for ASD.' If the value is less than the lower threshold, then the device output is 'Negative for ASD.' If the available information does not allow the algorithm to render a reliable result, the device output is 'No Result.'

SUMMARY OF NONCLINICAL/BENCH STUDIES

The Cognoa ASD Diagnosis Aid is a SaMD implemented on a general purpose computing platform. Non-clinical or bench testing was generally not needed to evaluate the hardware that the software is intended to be run on. Software documentation and a usability assessment were both provided to demonstrate the safety and effectiveness of the device.

SOFTWARE/CYBERSECURITY

Software verification and validation testing and documentation was provided according to a MODERATE level of concern and FDA's guidance document, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" (May 11, 2005), to demonstrate that the device software performs as intended. Adequate documentation describing the software, firmware, software specifications, architecture design, software development environment, traceability, revision level history, and unresolved anomalies conclude that the software will operate in the manner described in the specifications. Hazard analysis characterized software and cybersecurity risks, including device malfunction, measurement-related errors, protection of patient data when stored or in transit (including data encryption), and unauthorized access by malicious end users. The submission describes verification and validation testing to address the potential hazards with satisfactory results. The device algorithm was provided describing how the data are collected and analyzed by the underlying model that is applied to produce the final device outputs.

Regarding the cybersecurity, the documentation included all the recommended information from the FDA guidance document, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices." This includes a threat model, cybersecurity mitigation information, an upgrade and maintenance plan, and other information for safeguarding the device algorithms.

HUMAN FACTORS-USABILITY

An observational, simulated use study was performed in order to evaluate HCP completion of critical tasks associated with use of the HCP Portal component of the

Cognoa ASD Diagnosis Aid. A total of [b) (4)] primary care providers who completed residency training in Pediatrics, Medicine/Pediatrics, or Family Practice and who see pediatric patients were tested. Participants performed critical tasks across anticipated use scenarios, including (1) login per the instructions in the labeling to ensure access to the HCP Portal using user-specific account information and ability to locate the indications for use, precautions and warnings in the HCP Portal Instructions for Use; (2) ensure access to the patient dashboard for viewing patient data, labeling, and HCP Portal log-out; (3) ensure completion of the patient questionnaire; and (4) to ensure the patient's results can be viewed and querying how the HCP interpreted the results provided for each available device output (Positive for ASD, Negative for ASD, No Result).

A test moderator facilitated the testing, provided information regarding the test procedures beforehand, and asked questions specific to each use scenario evaluated. Specific to scenarios testing the use and interpretation of the device outputs, participants were asked to access patient records, discuss their clinical interpretation of each device output, and discuss how they would proceed with clinical decision making, both in the event that the device output affirmed or differed from how the patient presented clinically. Following completion of testing, post-evaluation interviews were conducted using 10 open-ended, neutrally worded questions to evaluate clinical end user perspectives of any use difficulties experienced during the testing.

Study results indicated that participants were able to complete identified critical tasks associated with use of the device. All participants understood and were able to navigate the labeling and recite or affirm understanding of the content. All participants were able to access patient records, complete the questionnaire and submit responses. All participants were able to access and review results, with 100% of participants reporting being able to communicate an accurate understanding of each type of device output. In response to probative inquiry, all clinical end users were able to communicate adequate understanding of use of the device as an aid in diagnosis of ASD and that the device does not provide a stand-alone diagnosis.

SUMMARY OF CLINICAL INFORMATION

Study Design
The clinical validation study was a prospective, double-blinded, single-arm study conducted at 14 sites in the United States ["Cognoa ASD Diagnosis Aid Validation Study"] to evaluate the safety and effectiveness of the Cognoa ASD Diagnosis Aid to aid in the diagnosis of ASD, with the comparator being the clinical reference standard. Both parents or caregivers and HCPs were blinded to the results as provided by the device. Additionally, the parents or caregivers, trained video analysts, and HCPs providing inputs to the device algorithm were blinded to data inputs provided by each other.

Clinical Reference Standard
The clinical reference standard is the determination of clinical diagnosis based on the majority assessment of up to three specialists. This involved diagnosis by a site-specific specialist using the DSM-5 criteria, followed by validation via independent review by one or two central specialist clinicians. After the diagnosing clinician on-site completed the patient assessment, the

patient case was reviewed by one central off-site reviewing specialist clinician who was provided with the standardized medical history and physical form, and a video of the diagnostic encounter. The diagnosing clinician was instructed to not state any diagnostic conclusion, decision on any particular component of DSM-5 criteria, or diagnostic observation during the video of the assessment. If the assessment of the reviewing specialist clinician agreed with that of the diagnosing clinician, the diagnosis was considered validated and no further validation was conducted. If the reviewing specialist clinician disagreed with the diagnosing clinician, then the case was referred to a second reviewing specialist clinician. Majority rule was used to resolve discrepancies between the two central reviewers and the site diagnosing specialist who all evaluated the same subjects.

Inclusion Criteria
- Caregiver must be able to read, understand and sign the Informed Consent Form (ICF).
- Caregiver or HCP concern for developmental delay.
- Female or Male, ≥ 18 to < 72 months of age.
- Functional English capability in the home environment.
- Caregiver must have smartphone capabilities for downloading the Cognoa Research App.
- Participants must be willing to be videotaped as part of the diagnostic assessment by the specialist clinician.

Exclusion Criteria
- Subjects with a prior diagnosis of ASD rendered by a healthcare professional.
- Subjects with suspected auditory or visual hallucinations or with prior diagnosis of childhood onset schizophrenia.
- Subjects with deafness or blindness.
- Subjects with known physical impairments affecting their ability to use their hands.
- Subjects with major dysmorphic features or prenatal exposure to teratogens (such as fetal alcohol syndrome).
- Subjects with history, suspicion, or diagnosis of genetic conditions (such as Rett's Syndrome or Fragile X).
- Subjects with microcephaly.
- Subjects with history or prior diagnosis of epilepsy or seizures.
- Subjects with a history of neglect.
- Subjects with a history of brain malformation, injury or insult requiring interventions such as surgery or chronic medication.
- Subjects whose age on the date of enrollment is outside the target age range.
- Subjects or caregivers who have been previously enrolled in any Cognoa clinical study or survey.
- Subjects whose medical records had been included in any internal Cognoa training or validation sets.

Objectives
Primary Effectiveness Objective

- Achieve a composite of positive predictive value (PPV) greater than 65% and negative predictive value (NPV) greater than 85% for the device in relation to the clinical reference standard in the overall study population; and
- Measurement of the proportion of all patients for whom the device provides no result.

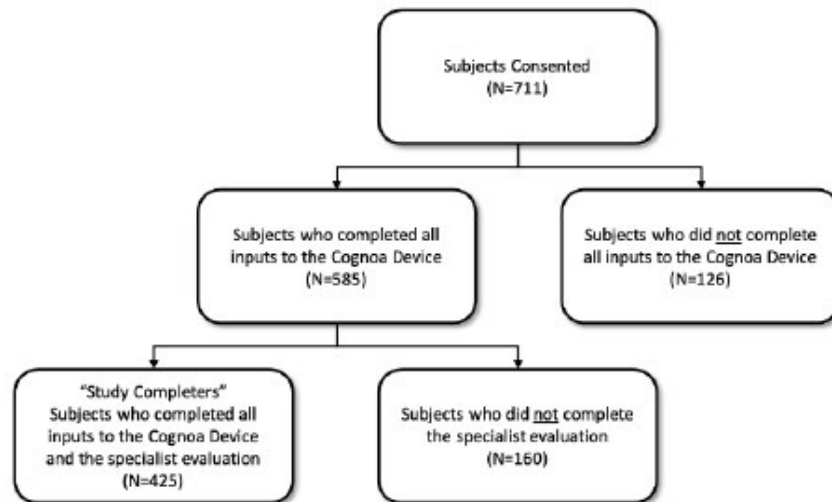*Secondary Effectiveness Objective*
- Evaluate sensitivity of the device in relation to the clinical reference standard in the overall study population; and
- Evaluate specificity of the device in relation to the clinical reference standard in the overall study population.

Safety Objective
Adverse events (AEs) and serious adverse events (SAEs) were collected and reported from enrollment through completion of the reference diagnosis clinic visit.

Results
Enrollment: A total of 711 subjects were enrolled who signed the ICF, with 585 subjects having completed all inputs to the device assessment. Of these 585 subjects, 425 subjects were considered study completers (i.e., subjects who completed both the device assessment as well as the specialist assessment per the clinical reference standard) (see Figure 1). The 425 subjects who completed all study assessments per protocol was used as the analysis population for the assessment of the study endpoints.

Figure 1. Study Subject Diagram

Effectiveness: Of the 425 subjects who completed both the device assessment as well as the specialist assessment per the clinical reference standard, the device rendered either a positive or negative diagnostic output in 135 subjects (32%). This corresponds to a 'No Result' device output rate of 68% (64%, 73%).

Measures of PPV, NPV, sensitivity, and specificity with associated 95% confidence intervals were calculated for <u>the subset of patients for whom the device rendered a diagnostic output of</u>

'Positive for ASD' or 'Negative for ASD', resulting in: PPV of 81% (70%, 89%), NPV of 98% (91%, 100%), sensitivity of 98% (92%, 100%), and specificity of 79% (68%, 88%) (see Tables 1 and 2).

Table 1. Results Comparing Device to Clinical Reference Standard

		Clinical Reference Standard		
		ASD Positive	ASD Negative	Total
Cognoa Device Output	ASD Positive	63	15	78
	ASD Negative	1	56	57
	No Response	58	232	290
	Total	122	303	425

Table 2. Statistical Estimates of Device Performance Observed in the Study

Metric	Point Estimate	95% Confidence Interval
PPV	80.77% (63/78)	70.27%, 88.82%
NPV	98.25% (56/57)	90.61%, 99.96%
Sensitivity	98.44% (63/64)	91.6%, 99.96%
Specificity	78.87% (56/71)	67.56%, 87.67%
No Response Rate	68.24% (290/425)	63.58%, 72.64%

Safety: No adverse events were reported during the study.

LABELING

The labeling is sufficient and satisfies the requirements of 21 CFR 801.109 for prescription devices.

The labeling includes a detailed description of the device with images and computing requirements that must be met by any general computing hardware to run the software device, a description of the patient population for which the device is indicated for use, warnings, precautions, and instructions for use. The labeling also includes summary information about the clinical validation study performed with the device. These discussions have been provided in both a user manual for physicians and a user manual for patients, parents, and caregivers.

The labeling includes warnings that the device is intended for use by healthcare professionals trained and qualified to interpret the results of a behavioral assessment examination and to diagnose ASD, and that it should be used in conjunction with patient history, clinical observations, and other clinical evidence the healthcare professional determines are necessary before making clinical decisions. For instance, additional standardized testing may be sought to confirm the device output, or especially for further evaluation when the device provides 'No Result'.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a pediatric Autism Spectrum Disorder diagnosis aid and the measures necessary to mitigate these risks.

Identified Risks to Health	Mitigation Measures
Device failure or incorrect analysis leading to: • False positives resulting in inappropriate patient treatment and potentially delayed diagnosis of a non-ASD condition • False negatives resulting in delayed diagnosis and patient treatment	Clinical performance testing Software verification, validation, and hazard analysis Labeling
Use error or misinterpretation of results resulting in a false positive or false negative	Usability assessment Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the pediatric Autism Spectrum Disorder diagnosis aid is subject to the following special controls:

(1) Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, including an evaluation of sensitivity, specificity, positive predictive value, and negative predictive value using a reference method of diagnosis and assessment of patient behavioral symptomology.

(2) Software verification, validation, and hazard analysis must be provided. Software documentation must include a detailed, technical description of the algorithm(s) used to generate device output(s), and a cybersecurity assessment of the impact of threats and vulnerabilities on device functionality and user(s).

(3) Usability assessment must demonstrate that the intended user(s) can safely and correctly use the device.

(4) Labeling must include:
    (i) Instructions for use, including a detailed description of the device, compatibility information, and information to facilitate clinical interpretation of all device outputs;
    (ii) A summary of any clinical testing conducted to demonstrate how the device functions as an interpretation of patient behavioral symptomology associated with Autism Spectrum Disorder. The summary must include the following:
        (A) A description of each device output and clinical interpretation;
        (B) Any performance measures, including sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV);
        (C) A description of how the cut-off values used for categorical classification of diagnoses were determined; and
        (D) Any expected or observed adverse events and complications.

(iii)A statement that the device is not intended for use as a stand-alone diagnostic.

BENEFIT-RISK DETERMINATION

The risks of the device are based on software verification and validation, and human factors-usability test data, as well as data collected in a clinical study described above.

The number of patients in the study who received a false negative device output was low (n=1). Risks associated with patients who receive a false negative result are mitigated by the device labeling, which states that a negative result does not ensure that the patient will not develop ASD in the future, and that performance of additional confirmatory assessment or testing among individuals with a negative result is at the discretion of the clinician. Similarly, the number of patients in the study who received a false positive was moderately low (n=15). Risks associated with patients who receive a false positive are mitigated by the device labeling, which reminds clinicians to always consider clinical presentation when making a diagnosis for ASD, and that such a diagnosis is based upon defined clinical characteristics outlined in the DSM-5. Furthermore, since the patients being evaluated by the device are already presenting with concerns of potential developmental delay as identified by either their parent, caregiver, or healthcare provider, patients who are incorrectly treated for ASD may still receive some benefit from these interventions, despite potentially delaying a correct diagnosis.

The probable benefits of the device are also based on software verification and validation and human factors-usability test data, as well as data collected in a clinical study described above.

Patients with true positive (n=63) or false positive results are likely to benefit from interventions for ASD. For true positive cases, getting a definite diagnosis can result in earlier confirmatory testing or assessment, in addition to earlier access to intervention. Currently, the average age of diagnosis for ASD in the United States is 4.3 years, as compared to 2.8 years observed in the pivotal trial of the Cognoa ASD Diagnosis Aid. Earlier confirmation of diagnosis can enable ASD patients to gain access to necessary intervention and optimize skill development at an earlier point in the neurodevelopmental window. Longitudinally, early intervention between 2 and 3 years of age has shown to result in positive outcomes upon reaching adulthood.

For patients who received a device output of 'No Result' (68.24% of subjects, or 290/425), additional standardized testing is recommended in order to drive clinical decision making. For patients who may be included that are ASD positive (n=58 in the study performed), the result may drive subsequent standardized testing and appropriate referrals, also in a more expeditious manner.

For the reasons described above, the probable benefits of the Cognoa ASD Diagnosis Aid outweigh the probable risks considering the listed special controls and general controls.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

> The Cognoa ASD Diagnosis Aid is intended for use by healthcare providers as an aid in the diagnosis of Autism Spectrum Disorder (ASD) for patients ages 18 months through 72 months who are at risk for developmental delay based on concerns of a parent, caregiver, or healthcare provider.
>
> The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process.

The probable benefits outweigh the probable risks for the Cognoa ASD Diagnosis Aid. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Cognoa ASD Diagnosis Aid is granted and the device is classified as follows:

> Product Code: QPF
> Device Type: Pediatric Autism Spectrum Disorder diagnosis aid
> Regulation Number: 21 CFR 882.1491
> Class: II