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Early identification and diagnosis of autism spectrum disorder: a literature review on evidence-based recommendations

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Abstract

Neurodevelopmental disorders correspond to a group of neurobiological-based clinical pictures. In the particular case of autism spectrum disorder (ASD), central difficulties are caused by deficiencies in communication/social interaction and by the presence of restrictive or repetitive behavior patterns. Diagnosis and treatment are currently based on behavioral criteria. According to data collected in different countries, at least 1 child out of 100 develops with some form of autism. Given the positive results associated with early interventions, for some years now, important efforts have been made with the aim of reducing the age of identification. In pediatric settings, familiarization with current diagnostic criteria, behavioral and etiological evaluation processes, and associated medical and behavioral conditions (sleep and eating disorders, seizures, gastrointestinal symptoms) affect the functionality and quality of life of the child and his family. To promote evidence-based practices on identification and diagnosis, several clinical guidelines and standards of practice have been published in different countries. The following article reviews and synthesizes these recommendations on the identification and diagnosis of ASD in the first years of life. This review has been carried out in light of recommendations from the international community that emphasize the need for evidence-based and culturally sensitive local programs and services, particularly in low- and middle-income settings.

Keywords:

MESH: Autistic Disorder; Behavior; /diagnosis; Early Diagnosis; Disabled Children

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Introduction

Autism spectrum disorder in an international context

One of the main challenges of the 21st century related to child health is the early identification of children with a neurodevelopmental condition, such as autism spectrum disorder. A late diagnosis involves denying a child or young person the opportunity to understand their responses to different situations. It also implies additional stress for the families, the delay in the diagnosis of other co-occurring conditions and an increase in financial costs for the family and society [1]. For this reason, several efforts have been made in recent decades to lower the age of diagnosis. For example, validation studies have been carried out on early detection tests in populations without risk, and information campaigns on early signs have been organized. In addition, national or international organizations have taken various initiatives to promote awareness of the needs of people with ASD and facilitate access to services based on scientific evidence, particularly in low- and middle-income countries where the participation of professionals, communities and authorities is considered important for the development of regional strategies that allow the dissemination of good practices in each country [2-4].

Two important factors have promoted this international awareness. The first has to do with the positive results of behavioral and educational interventions (see, for example [5]), whose impact is described as particularly important during the first years of life [6, 7], with statistically significant improvements in aspects of language, cognitive skills and adaptive skills [8, 9]. Although the stability of a diagnosis in the early years is a delicate aspect that requires further investigation [10], it is considered that an accurate diagnosis is possible from the second year of life [9] and would be stable from 14 months of age, as suggested by the results of a study conducted in the general population with 1,269 participants aged between 12 and 36 months [11]. Access to early intervention services would then, for the moment, be the best way to develop the skills of people with autism and would also represent the best cost-benefit ratio for families and for society.[12, 13].

The second factor has to do with the considerable increase in the number of people diagnosed with autism around the world. Indeed, estimates have gone from 0.04% in the 1970s to 1-2% today. Among the factors that contribute to the explanation of this increase in prevalence would be the improvement in diagnostic practices, the increase in the number of trained professionals, the inclusion in the studies of individuals without intellectual disabilities, and the changes in diagnostic criteria of the fourth revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [14] to the fifth edition (DSM-5) [15]. The lack of estimates from different regions of the world, particularly from regions with low and middle income, has led to the acceptance of an estimate of 0.6% in an international context.[16] However, more recent studies suggest prevalence estimates of between 1% and 2% of the population, as in Australia (1.02%) [17], the United States [1.85%) (18), and England (1.76%) [19]. Estimates can vary considerably between regions of the world, between studies, and over time, and these differences can be explained by participant recruitment methods, sampling techniques, the presence of inconsistencies in the definition of autism cases, the inclusion criteria adopted by the researchers or by the degree of qualification of the professionals who evaluate the cases.

In South America, studies carried out in Argentina [20] and Colombia [21] report lower estimates than most high-income countries [16], which suggests that a significant number of children in these countries have not been identified and may not have access to ade-quate services. In Ecuador, where the legal framework provides a certain number of rights for people with ASD[22], preliminary evidence published in 2015 based on the responses provided by directors of schools in the city of Quito estimated that the school attendance of children diagnosed with ASD corresponded to 0.11% among 453 students from 161 regular schools [23]. The reason these estimates are notably lower than international estimates has not, to our knowledge, been studied.

The study of autism

The insights that have improved understanding of this spectrum of conditions come from various disciplines.

On the one hand, medical neurosciences and neurophysiology have provided a framework for studying the development of their symptoms and their impact on behavior (see, for example [24]). Work in genetics with molecular and sequencing approaches has made considerable efforts to provide explanations of the behavioral phenotype and has contributed to identifying more than 100 genes involved, of which most would affect synapses, excitatory or inhibitory events, and the regulation of others genes [25]. Cognitive neurosciences have provided specific experimental instruments for the study of perceptual-cognitive mechanisms, such as those that play a role in the identification of social information, the emotional content of faces or the ability to spontaneously address others people, whose study is carried out with the ambition of lowering the age of diagnosis of autism [26, 27]. On the other hand, intercultural studies have facilitated awareness of the impact of socioeconomic and cultural contexts on the identification of symptoms, both in the diagnostic process and in families' help-seeking behaviors [28] or in the feeling of self-efficacy of the professionals [29]. This multidisciplinary vision has been indispensable in trying to respond to the challenges associated with early detection and diagnosis, and it is of particular importance outside the predominantly Anglo-Saxon contexts that have given rise to theories and practices now used around the world.

Table 1 Degree of evidence of practices for the diagnosis of	ASD
(adapted from Volkmar et al., 2014 [<u>30</u>].	

Degree of Evi- dence	Application
Clinical standard	It applies to recommendations that are
	leg meta-analyzes systematic reviews
	individual randomized controlled trials)
	and / or strong clinical consensus.
Clinical guide	It applies to recommendations that are
	based on strong empirical evidence (eg,
	non-randomized controlled trials, cohort
	studies, case-control studies) and / or
	strong clinical consensus.
Clinical option	It applies to recommendations that are
	based on emerging empirical evidence
	(eg, uncontrolled trials or case series) or
	clinical opinion, but lack strong empirical
	evidence and / or strong clinical consen-
	SUS.
Not approved	Applies to practices known to be ineffec-
	tive or contraindicated

This body of knowledge that has been released now allows the production of recommendations on good practices. However, recommendations for clinical practice should be established taking into account the strength of empirical or clinical support available to them. For this, the diagnostic practice parameters, such as those described by Volkmar et al., 2014, can be very useful (see table <u>1</u>).

Methodology used in this review

Although there are works that summarize the current state of knowledge in Spanish, these are limited in number [31] or are they currently in the process of updating [32]. The vast majority of peer-reviewed clinical practice guidelines on the diagnosis of ASD in children have been published in English-speaking countries, which could constitute a difficulty in accessing information in the Spanish-American region. (For a systematic review of documents of clinical guidelines for the diagnosis of ASD in English-speaking health systems and financed by public funds see [33]). The purpose of this narrative review is to extract and synthesize the identification and diagnostic processes described, which could be adapted to an Ecuadorian context or to that of countries in the region that share similar characteristics and challenges.

The process of developing this review took into account the opinions of professionals in pediatrics and family medicine who were interviewed in 2018 with the cooperation of the Ecuadorian Society of Pediatrics and the Department of Pediatrics of the Pontificia Universidad Católica de Quito [3 4]. This process also included a consultation with representatives of families of people with ASD in Ecuador, consistent with current perspectives on the promotion and rights of people with special needs, for example, the 2006 United Nations Convention [35], according to which the work guidelines should not be decided without the participation of representatives of the groups affected by those guidelines.

This literature review was carried out during the period from May 2019 to January 2021. It was carried out based on the narrative review methodology, which synthesizes the knowledge of previous publications with a focus on new areas of study not yet addressed. [36] and following the model used by Hayes et al. in

2018 [37], which allows the extraction of key data related to the diagnosis of autism but at the same time facilitates the reading of the recommendations as a coherent set of texts that shape the diagnostic process. To limit biases, the scientific literature search methodology was inspired by the PRISMA approach, that is, based on a systematic review in terms of keywords, titles, abstracts and data extraction techniques [38]. An electronic search was then carried out, taking as inclusion criteria the date of publication from 2010, for 'practice guides', 'reviews' or 'practice parameters'. This search was carried out in several databases: National Institute for Health and Care Excellence (NICE), The Cochrane Library, PubMED and PsycINFO. The following search terms were used: 'autism', 'autism spectrum disorder', 'identification', 'detection', 'screening', 'evaluation', 'practice', 'clinical', 'guide', 'protocol', 'strategy', 'parameter' AND 'age group: preschool', AND 'peer-reviewed newspapers' in publication type, with' language 'English' and 'Spanish' as advanced filters. On the other hand, a search was carried out in relevant pages of international (WTO) and regional (PAHO) health agencies. The revised texts come from various regions of the world: Canada [12, 39, 40], the United Kingdom [41], the U.S. S [13, 30], Australia [42] and France [43]. Finally, a data extraction framework was created to identify key characteristics of the screening and diagnostic processes based on the needs reported by parents and professionals in the Ecuadorian context, particularly related to the following elements: identification tools; early diagnostic process; professionals involved in the diagnosis; comorbidities; contribution of studies in neuroimaging and metabolic tests and genetic studies; and particularities related to the diagnosis of autism in girls. The results of this synthesis are presented in the second part of this work. In the first part, we will present general information about ASD.

Current definition

ASD refers to a complex variety of neurodevelopmental difficulties that persist throughout life. The significant phenotypic heterogeneity in ASD is reflected in the various levels of severity of the manifestations, which can range from slight differences in communication skills to severe disability [44]. Symptomatic heterogeneity is also present in intellectual and adaptive functioning, as well as in the existence of comorbidities. The latter have been described, for example, in sleep regulation, eating behaviors, digestive difficulties and emotional regulation [45]. The consistency of this condition results from the presence of a main group of symptoms that allow its identification. These diagnostic criteria have been collected in two classification systems: DSM-5[44] and ICD-10 [46], with the imminent updated publication of the ICD-11 [47].

Table 2 Advertising and consumption of processed products.

A. Persistent deficiencies in social communication and social interaction in various contexts, manifested at present or by the antecedents of their history (illustrative, but not exhaustive examples):

1. Deficiencies in socio-emotional reciprocity vary, for example, from abnormal social closeness and failure of normal two-way conversation, through decreased interests, emotions, or affections, to failure to initiate or respond to social interactions.

 The deficiencies in non-verbal communicative behaviors used for social interaction, vary, for example, from poorly integrated verbal and non-verbal communication, through anomalies in eye contact and body language or deficiencies in understanding and use of gestures, up to a total lack of facial expression and non-verbal communication.
 The deficiencies in the development, maintenance and understanding of relationships vary, for example, from difficulties in adjusting behavior in diverse social contexts, through difficulties in sharing imaginative games or in making friends, to the absence of interest in their peers your age.

B. Restrictive and repetitive patterns of behavior, interests, and activities, manifested in two or more of the following pints, currently or by background (the examples are illustrative, but not exhaustive):

1. Stereotyped or repetitive movements, use of objects, or speech (eg, simple motor stereotypies, alignment of toys or moving objects, echolalia, idiosyncratic phrases).

 Insistence on invariance, excessive inflexibility of routines or ritualized patterns of verbal or non-verbal behavior (eg, great distress in the face of small changes, difficulties with transitions, rigid thought patterns, greeting rituals, need to drink the same way or eating the same foods every day).
 Very restricted and fixed interests that are abnormal in terms of intensity or focus of interest (eg, strong attachment or preoccupation with unusual objects, overly circumscribed or persistent interests).

4. Hyper- or hyporesponsiveness to sensory stimuli or unusual interest in sensory aspects of the environment (eg, apparent indifference to pain / temperature, adverse response to specific sounds or textures, excessive sniffing or palpation of objects, visual fascination with lights or movement).

DSM-5

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the North American Psychiatric Association lists the standardized criteria for the diagnosis of ASD. [44] (see Table 2). This system no longer conceives of autism as a series of independent disorders, as was the case in its previous version, the DSM-IV-TR [48], and as is still the case in the International Classification of Diseases (ICD-10). Indeed, the old definition considered different categories: autism disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder unspecified (PDD-NOS).

The new definition results from a scientific consensus, which considers these disorders as part of a single-dimensional condition, with variable levels of severity of symptoms and the level of development reached, therefore showing differences in the level of support required by an individual at the time of diagnosis. These symptoms correspond to two central areas: (i) deficits in social communication and social interaction and (ii) restriction of behaviors and interests and the presence of repetitive behaviors, specifying that in cases where this second area is absent, these would be classified as "social communication disorder." This new version encourages health and research professionals to specify individual characteristics. Indeed, it is requested to specify the presence or absence of intellectual disability and language problems. It is also necessary to specify whether autism is associated with a known medical or genetic condition, an environmental factor, a neurodevelopmental disorder, a mental disorder or a behavioral disorder. This version also indicates that symptoms must be present in early childhood, although they may not become clear until social demands exceed the person's capabilities.

The symptoms must cause a clinically significant impairment in social, occupational, or other important areas of the person's functioning and must not be better described by another DSM-5 diagnosis.

In addition, this version introduces a series of specifiers to provide information related to the current presentation of symptoms in a person who meets the criteria for ASD. The use of these specifiers is in some way intended to replace the old multiaxial system. This translates the effort to include topics and descriptors that are applied in a transdiagnostic way.

The first of these specifiers reports the eventual presence of a known etiological factor, that is, a medical condition, a genetic syndrome or an environmental factor. The second specifier describes the level of support required and the impact of symptoms on different levels of a person's functioning. This ranges from levels 1 to 3, indicating a need for support, substantial support, or very substantial support, respectively. These levels correspond to the need or to the type of services required; however, they do not specify the profile of capabilities of a person or an individual hierarchy of intervention objectives. The third specifier allows us to indicate whether there is intellectual disability. The fourth specifier indicates whether there is a language disability in the receptive and expressive aspects, also giving a concise description of the actual linguistic abilities that the individual possesses. The last specifier allows you to indicate whether catatonia is present.

It is important to note that this new definition of autism has legitimately raised parental concerns about the disappearance of the "Asperger" category. [49], since in some national health systems, the diagnosis of autism would be required for the coverage of intervention services. It is also important to note that the DSM-5 indicates that persons with a well-established DSM-IV diagnosis of Autistic Disorder, Asperger's Disorder, or Unspecified Pervasive Developmental Disorder should now be diagnosed with Autism Spectrum Disorder.[50]

Finally, it should be noted that this diagnostic system has been updated more frequently than the International Classification of Diseases system of the World Health Organization (WHO) since it does not depend on complex international consensus and agreements. The differences between the two systems have led to complications in clinical definitions and research. Indeed, researchers in many countries around the world use the DSM, but the ICD would be the most widely used coding system in clinical practice.

ICD-11

The publication of the International Classification of Diseases (ICD-11) will enter into force on January 1, 2022 and will expire the ICD-10 conception of autism, based on the literature developed in the eighties. The current DSM-5 and ICD-11 classifications of autism are close in

several respects. First, the two classifications include autism in the category of neurodevelopmental disorders, indicating that they involve significant difficulties in the functioning of certain social, sensorimotor or intellectual skills. Second, the two systems group autism symptoms into two main areas: i) persistent deficits in the ability to initiate and maintain reciprocity in social interaction and communication and ii) the presence of restricted, rigid and repetitive behaviors and interests, with difficulties present in all the person's living environments, although the severity of the symptoms may vary according to the social or educational context and generate a negative impact on the personal, family, social, educational or occupational context. On the other hand, the ICD-11 also recognizes the variability in the spectrum of intellectual and language functioning but does not propose a descriptive classification of severity as in the DSM-5 but rather formulates a series of subdivisions (Table 3). It also proposes two other categories, (6A02. Y / 6A02. Z) for "other" specified autism spectrum disorder and for a "nonspecific" autism spectrum disorder. Unlike DSM-5, and a significant part of the literature, the CDI-11 does not include hyperresponsiveness or hyporesponsiveness to sensory stimuli, nor does it include unusual interests or behaviors in relation to sensory aspects of the environment. Finally, it should be noted that the section on language development includes a category related to pragmatic language deficiency, which would correspond to the DSM-5 Social Communication Disorder.

 Table 3
 Subdivision of ASD disorders (6A02) according to ICD-11
 [47]

	Intellectual disorder	Functional language defi- ciency
6A02.0	No disorder	No disorder
6A02.1	With disorder	No disorder
6A02.2	No disorder	With disorder
6A02.3	With disorder	With disorder
6A02.4	No disorder	Absence of functional lan-
6A02.5	With disorder	guage Absence of functional lan- guage

In conclusion, the description in the DSM-5 and the imminent publication of the ICD-11 should contribute to harmonizing the diagnosis in children and adults, significantly clarifying the situation for professionals and families. Furthermore, the harmonization of the diagnostic criteria between these two systems will allow the reception of research from different countries and equalize the findings of different studies.

Etiological hypotheses

The identification of environmental factors, which could be related to a higher prevalence of ASD, has been an active area of study for several years. Factors have been investigated at the prenatal level (short intervals between pregnancies, multiple gestations, maternal obesity, gestational diabetes, parental age and infections, etc.) and at the perinatal level (premature deliveries, low birth weight, fetal growth restriction, intrapartum hypoxia and neonatal encephalopathy) [51]. The influence of in utero exposure to drugs such as valproate and thalidomide or organophosphates and other pesticides, metals, volatile organic compounds and air pollution, particularly nitrogen dioxide, has also been examined [52]. Although some of these factors could increase the risk, the numerous studies carried out have not yet made it possible to reach clear conclusions [53].

On the other hand, a significant amount and variety of data currently provides strong indications about the genetic contribution to the risk of ASD (see [13]). The impact of genetic factors on autism has been studied since the 1970s. More recent studies, carried out in groups of twins in different countries, point out the importance of heritability with estimates of 64% to 91%, and a meta-analysis, which included 6413 pairs of twins, revealed a concordance of 98% in monozygotic twins and a concordance of 53% to 67% in dizygotic twins [54, 55]. Other studies also highlight the situation of fraternal siblings, who may present symptoms related to ASD but do not meet the threshold for a diagnosis, which has been described as the "expanded phenotype of autism." [13, 56, 57]. Currently, scientific consensus on etiological hypotheses is established around a complex interaction between genetic factors and environmental factors [58].

Barriers to identification

The significant heterogeneity in the etiology, the age of onset of the first symptoms and the developmental trajectory makes ASD a difficult-to-detect condition [59]. In addition to these difficulties inherent in the condition, there are other, more subjective factors that act as obstacles to early detection. Thus, for example, the way a family interprets symptoms has been described as a barrier in several countries. Indeed, a study carried out in a Mexican-American context suggests that a reduced frequency of social initiations directed at adults could be understood, in this context, as a sign of courtesy [<u>60</u>]. In the same way, a lack of response to the instructions of adults can be interpreted as a voluntary act linked to the child's personality and, therefore, not worrying those around him [<u>61, 62</u>].

Other barriers have been identified in professional contexts. For example, the difficulty of accessing screening instruments adapted to the age and situation of the child [63] and the insufficient number of trained and experienced professionals, particularly in developing countries [29], as well as the risk that professionals do not use standardized instruments in the absence of parental concerns [64]. In Ecuador, certain barriers, also described in other contexts, such as the lack of time to apply a screening, the lack of resources adapted to their daily practice, and the need to acquire knowledge, were reported in 2019 based on a group of 183 pediatricians and family physicians as major obstacles to case identification [3, 4]. In Latin America, a study carried out in 2020 in Brazil, Argentina, Chile, Uruguay, Venezuela, and the Dominican Republic simultaneously indicated that the main barriers to access to services reported by families were long waiting lists (50.2%), treatment costs (35.2%) and lack of specialized services (26.1%) [65].

Identification and diagnosis

It is highly probable that globally, the age of diagnosis is later in settings with medium or low resources with populations without access to public or private insurance coverage than that which is reported in contexts of high resources [<u>31</u>]. Therefore, development monitoring or surveillance is promoted by the WHO as a useful process, particularly in low- and middle-income countries [<u>4</u>].

The practices of early detection of ASD are also considered clinical standards by national health authorities, as in the United States [30], and both the monitoring of "warning signs" and the use of screening instruments are also supported by the practice parameters of the American Academy of Pediatric Neurology [66] and by the guidelines of the American

Academy of Pediatrics (AAP), who suggest routine monitoring of ASD symptoms at 18 and 24 months of age, in addition to well-child check-ups at 9, 18 and 30 months of age [<u>13</u>, <u>67</u>]. This view, which considers screening tools as important for gathering information on signs and/or symptoms of ASD in a structured way, is shared by the Australian guidelines for evaluation and diagnosis [<u>42</u>]. In France, the monitoring of warning signs by professionals who provide regular care to the child (general medicine, pediatrics or school medicine) is suggested during mandatory check-ups in children from 0 to 6 years old [<u>43</u>].

Table 4Examples of "Warning signs." Adapted from "AutismSpectrum Disorders (ASD). Signs and Symptoms." Centers forDisease Control and Prevention (CDC) [68]

Warning signs Does not respond to his name by the time he is 12 months old Not pointing to objects to show interest (for example, an air-plane in flight) by the age of 14 months Does not play "pretend" (pretending to "feed" a doll) by the time he is 18 months old Avoid eye contact and want to be alone Has delays in the acquisition of speech Repeats words or phrases over and over again (echolalia) Give answers unrelated to questions Shows irritation to minor changes Has restricted interests Flaps hands, rocks, or spins in circles Has unusual reactions to the sound, smell, taste, look, sound of things

For its part, the Canadian Pediatric Society emphasizes developmental surveillance, with an approach based on monitoring parental concerns and child observation, with or without standardized tools [12]. In addition, within the framework of awareness campaigns on developmental difficulties, lists of warning signs that are accessible in Spanish have been made available to professionals and the general public, such as "Learn the symptoms. Act Soon" from the US Centers for Disease Control and Prevention (CDC) [<u>68</u>] (see Table 4).

Pediatric professionals are called upon to play an important role. By having constant contact with the family of young children, they can establish a direct and meaningful relationship with it [<u>69</u>]. Their involvement in the screening process is a fundamental issue for the efficient management of ASD cases, which ranges from development monitoring to diagnosis, passing through the transmission of information on the existing supports for central symptoms and the followup of possible comorbidities [<u>70</u>].

In that context, a major impact will come from careful attention to parental concerns $[\underline{41}]$, as well as the observation of social and communication skills during consultation with young children $[\underline{12}, \underline{43}]$.

Screening Tools

Currently, there is no recommendation on a single instrument for screening cases of ASD, but there are several validated instruments from which professionals can choose, depending on the age of the child [71]. Although not all children who develop ASD exceed the cut-off points of these instruments and not exceeding these criteria can automatically rule out a diagnosis of ASD, studies carried out in high-income countries suggest that their use during routine visits can lead to more accurate and earlier identification compared to the exclusive resource of clinical impression [72].

The existing variability of instruments is reflected in the different practice guides consulted. Some explain the screening process without mentioning particular instruments [41], while others mention instruments adapted to their context [12] or make available a list of instruments and their characteristics [13, 40, 43]. In settings with low- and medium-resource populations, however, a crucial issue is to avoid the introduction and dissemination of low-quality screening instruments [73]. The validation of instruments is a long and expensive process, and it presents several challenges, from the collection of evidence (e.g., absence of crosssectional studies or validation studies exclusively in clinical populations) to the absence of consideration of the lack of services or support structures for the populations to be diagnosed [74]. It is also important to take into account that the psychometric qualities of the instruments may vary in sociocultural contexts different from those where they were developed, so their use should not be exclusive and should be accompanied by a qualified clinical impression.

Screening instruments also vary significantly in relation to the time required for their use and the cost

of acquisition, but they are considered easy to apply, and some are free. Most likely, the tool with the most validation studies is the Modified Checklist for Autism in Toddlers, Revised, with Follow-Up (M-CHAT-R/F) [75, 76]. This questionnaire was adapted from the British version CHAT[77] to facilitate administration in pediatric and community care settings for children 16-30 months and has a sensitivity of 0.77–0.97, a specificity of 0.38-0.99, and a positive predictive value of 0.06-0.92 [12]. The revised version with follow-up (M-CHAT-R / F), which eliminates 3 questions in relation to the previous version, provides three types of classifications. First, scores below 3 are considered risk-free. Second, children who score 8 or higher are classified as high risk for ASD or another developmental disorder and must be referred immediately for diagnostic evaluation and early intervention. Finally, children with scores from 3 to 7 will require a brief follow-up interview to clarify the elements classified as positive [76]. The validation study found that children whose total score was \geq 3 initially and \geq 2 after follow-up had a 47.5% risk of being diagnosed with an autism spectrum disorder and a 94.6% risk of presenting any developmental disorder, delay, or concern [76].

Various adaptation and validation efforts have been made to make these instruments available to Spanish-speaking populations. Indeed, there are studies on the versions of M-CHAT, both in Spain [78, 79] and in Spanish-speaking America, in Mexico [80], Argentina [81] and Chile [82], with results that report different levels of sensitivity and specificity. In addition, other important works are currently being carried out in Latin America and Spain, such as the Q-Chat study [83], which aims to quantify the autistic traits of children between 18 and 30 months in a Chilean population [74], or the adaptation of the SACS-R, developed in Australia for use in a Spanish population (personal communication).

Early diagnostic process

Screening instruments are not designed to confirm a diagnosis but are intended to alert to the possibility that a child is developing with autism. In the event of a significant presence of symptoms, the child will be referred for an evaluation process that requires observation of various aspects within the framework of a clinical diagnosis [31].

The first aspect in the evaluation process is the establishment of the medical history, which includes family history, prenatal and perinatal data, a history of evolution of developmental milestones, medical history, presence of factors associated with an increased prevalence of autism [41, 43], a physical examination to document growth parameters (particularly head circumference) and the presence or absence of dysmorphic features, current and past treatments, as well as contextual data to assess supports and challenges in the child's environment [12, 42].

The second element in this process is the specific study of symptoms through instruments that help determine the presence and impact of symptoms on the functionality of a child [39]. On the one hand, there are instruments to collect information on developmental history through interviews with caregivers and reports on behavior in other settings (such as school). In some clinical settings, information gathering can be done with parent interviews, such as the Autism Diagnosis Inventory Revised (ADI-R) [84, 85], with the Social Communication Questionnaire (SCQ) [86], with the Social Response Capacity Scale (SRS) [87], or with the Inventory of Symptoms of Autism in Young Children [88]. These instruments constitute a structured approach that can assist an experienced clinician in the application of diagnostic criteria, although none alone can reach it [13]. On the other hand, there are instruments for structured observation of symptoms, which can be used in some contexts to support the application of diagnostic criteria during a clinical evaluation.

Although at the moment there is no single tool suitable for all clinical settings, there are studies on the psychometric properties of some instruments. For example, a Cochrane review on diagnostic tests for ASD in preschool-age children that compares the Autism Diagnosis Observation Scale (ADOS) [89], the Childhood Autism Rating Scale (CARS) [90], and the ADI-R concludes a higher sensitivity of ADOS and an equivalent specificity of all these instruments [91]. Regarding the practice guides, some of them describe the processes without mentioning a particular instrument [30, 41], others make available a list of screening and evaluation instruments [13, 42] and others point to instruments that have shown good reliability and validity [39, 43].

It is important to note that most diagnostic instruments have been developed in English-speaking countries, have a high cost and/or require specialized training. Although their validity outside the settings in which they have been produced can be questioned, their use has been tested in research and clinical contexts and in a significant number of people. Currently, work is being carried out that is beginning to lay the foundations for intercultural validity, for example, in the case of ADOS-2 in South Africa, where a study has concluded on the adaptability of the materials and activities used in this context [92]. In all cases, taking into account the lack of validation in Latin American contexts, it is important to remember that no instrument should be used in isolation to make a diagnosis. A clinical judgment of professionals with experience and specific training will also be necessary based on the information obtained from all the necessary sources [39]. It is also important to take into account the developmental perspective, that is, to consider the impact of chronological age and developmental age on the presentation of symptoms; for this reason, solid knowledge about typical development is necessary [42].

With regard to very young children, there has been, for some years, a better understanding of the presentation of symptoms during the first two years of life. However, knowing that the diagnostic decisions made for children of that age are less stable than those made for children approximately 3 years of age [93]. A priority for the field of study of early identification is to ensure that professionals are adequately equipped to handle these types of evaluations. This finding has stimulated the production of instruments for experienced clinicians to quantify behaviors and establish "ranges of concern," which allow reflecting the diagnostic uncertainty, which is often faced in the evaluation of very young children, either due to developmental variability or confounding factors (such as global developmental delay or early language impairment), but which allow, at the same time, to respond precisely to the priority of early intervention [94].

A third step is the evaluation of the linguistic (expressive and receptive), cognitive, adaptive and psychomotor aspects [<u>12</u>, <u>13</u>, <u>41-43</u>], which have a great impact on the functioning of a person, on their prog-

nosis [95] and are also necessary for a differential diagnosis [41] (for a list of examples of available materials, see [31]). It is important to take into account that the developmental profile of people with autism can have significant intraindividual variability. In this sense, a cognitive assessment that leads to a global IQ number may not accurately reflect their functional capacity without also taking into account that, in certain cultural contexts, the numerical result obtained could contribute to the stigmatization of a person, particularly in a school environment. Rather, the assessment should focus on identifying specific areas of individual strengths and weaknesses that will serve as the basis for the development of an intervention plan and appropriate work strategy recommendations.

Finally, it will also be necessary to evaluate any emotional or behavioral difficulties and the examination of sensory aspects (hearing and vision), as well as the neurological examination (see below: Contribution of imaging studies and metabolic and genetic tests)

In addition to these elements, there are a number of factors that must be taken into account during an evaluation process. For example, it is important to remember that certain difficulties in social interaction may not manifest themselves in the first 2 or 3 years of age, so their absence should not rule out a possible diagnosis [15]. On the other hand, when there are warning signs, a diagnosis of autism should not be ruled out by the simple presence of good eye contact, a smile or signs of affection to family members [41]. It should also be taken into account that in some contexts, in case of uncertainty, an ASD diagnosis will be preferred to another if the clinician considers it in the interest of the patient, for example, for cultural reasons (stigma) or access to services (treatments or supports) [37]. Finally, it is important to remember that a categorical diagnosis of ASD by itself does not establish the types of treatment necessary for a person; for this reason, the clinical diagnosis must be individualized, adapted to the context and must take into account the limitations caused by the symptoms, but also the skills and strengths of the individual that will guide decisions about treatment, supports and guidance for families [<u>13</u>, <u>39</u>, <u>40</u>, <u>42</u>, <u>43</u>].

When it comes to prognosis, it is variable. However, certain authors have observed that more than 80% of children under 3 years of age diagnosed with ASD through a complete evaluation retain their diagnosis, and just over 9% do not meet the diagnostic criteria for ASD in early adulthood [96, 97]. Two observations should be underlined in this regard. First, longitudinal studies suggest that symptom severity scores are more likely to improve in individuals who show significant development in verbal IQ (Gotham, 2012) [98]. In addition, no longer meeting the criteria after childhood would be related to a good development of cognitive skills at two years of age, having received intervention in their early years and having shown a decrease in their repetitive behaviors over time [95]. The second observation is that a better quality of life in adults with ASD would be more associated with the existence of a breadwinner from their family and their community than with the characteristics of their symptoms [95], which highlights the fundamental role of the supports provided by the socioeconomic environment in which an individual and his family develop.

Finally, it should be mentioned that there are descriptions of changes in diagnosis throughout development. For example, a diagnosis of obsessive compulsive disorder would be more likely in children who were diagnosed with ASD before 30 months of age or who had a diagnosis of PDD-NOS according to the DSM-IV Wiggins, 2012 [99]. However, these conclusions need further studies to be expanded and clarified. Similarly, more research is needed on the evolution of phenotypic subgroups or demographic subgroups, such as groups of girls and ethnic subgroups

Professionals involved in the diagnosis

The etiological and phenotypic variability, as well as a symptomatology that evolves with age, contribute to the complexity of the diagnosis, for which in many cases the experience and knowledge of professionals from various specialties is required. Within this framework, pediatric and community medicine professionals play a fundamental role in identifying the first signs of ASD and ensuring a timely diagnosis [12]

Although the current consensus for the diagnosis is the participation of a multidisciplinary team ('gold standard') [100], the qualification of the different professionals involved varies from one country to another. Some guides are particularly explicit in the type of training, the degree of experience, and the records required [42], others describe their composition to a greater or lesser degree [12, 13, 30, 39, 40, 43] or require the need for a reference professional, such as a pediatrician or a psychologist, a speech therapist with extensive training, in addition to the presence or regular access to a pediatric neurologist, a psychologist and an occupational therapist as appropriate [41].

The availability of adapted services is a challenge that requires planning and monitoring by different actors involved in the implementation of good practices in all contexts. For example, in Great Britain, the British Medical Association requests that adequate funding be available to ensure that wait times are no longer than three months for an initial diagnostic evaluation and to be able to meet national standards on autism patient care [1]. In other socioeconomic contexts, the limited availability of trained professionals could make it difficult to set up multi- or multidisciplinary teams, and the level of available resources could require adaptations. In the case of Ethiopia, for example, one study identified 60 psychiatrists across the country as potentially qualified personnel for autism case management, two of whom were child psychiatrists [101]. The response, in this context, was to offer training to community health workers based on an adaptation of the World Health Organization's Skills Training for Caregivers program [102].

The need for highly qualified professionals, although desirable, can result in a high cost for families when health systems have not provided coverage in terms of evaluation and intervention [29] and can significantly impact waiting times, as reported, for example, in some Canadian regions [39, 41].

Taking these limits into account, the Canadian Pediatric Society, in its position on the diagnostic evaluation standards for ASD in 2019, proposes a flexible model based on the idea that more pediatric professionals should be trained in the diagnosis of fewer cases. complex, from maintaining to reducing the waiting times from 1 year to the 3-6 months of waiting suggested in this context [39]. This model has three approaches that allow taking into account the complexity of the symptoms, the medical and psychosocial history of the child, the clinical experience and the judgment of the pediatric professional and could, subject to adaptation to local particularities, be used in contexts in those in which diagnostic specialists are scarce. The first approach corresponds to the traditionally recommended interdisciplinary or multidisciplinary teams. The interdisciplinary teams work collaboratively in an integrated and coordinated way, while the members of the multidisciplinary team work independently from each other but share information with the aim of reaching a diagnostic decision by consensus. This approach would be particularly useful when referred children have factors that make diagnosis difficult, such as subtle symptoms, coexisting health problems, or when there is a complex medical or psychosocial history. This approach has the advantage of helping to capture useful information for planning and optimizing treatments and can increase the certainty of the diagnosis, but as previously mentioned.

The second approach is that of shared care and joint responsibility. In this case, a pediatric professional can use the information collected during the observation carried out with a diagnostic instrument and, in parallel, consult with an evaluation specialist to inform the diagnosis. This approach, which involves the exchange of information and clinical knowledge about the patient, is suggested for children under 2 years of age or with a mild, atypical or complex presentation of symptoms.

The third approach is that of a single vendor. In this case, an experienced or trained pediatric professional can diagnose ASD independently, based on clinical judgment and according to DSM-5 criteria, with or without data obtained using a diagnostic assessment tool. This approach, suggested when a child's symptoms clearly indicate ASD, has the advantage of alleviating waiting times, but it has limitations in relation to the certainty of the diagnosis, and in some jurisdictions, it is not sufficient to access specialized services.

In all cases, and regardless of the approach adopted, collaboration between professionals and the consent of families to share information should allow the precision of the diagnosis and avoid duplication of efforts. In all cases, professionals in charge of the diagnosis must take into account the available and adequate resources to refer the child and his family and to support the implementation of the necessary intervention.

Contribution of studies in neuroimaging and metabolic and genetic tests

There is a significant body of work exploring neurobiological, genetic, chemical and cognitive factors that may, in the future, provide biomarkers for the diagnosis of autism (see, for example, [103]). According to some studies, neuroimaging tests have not confirmed that clinical findings are more common in ASD than in other neurodevelopmental disorders, and specific abnormalities would not correlate with clinical, etiological or pathophysiological aspects of ASD [13, 104]. The indication for an MRI should be guided by a medical history and a physical examination and may be necessary, for example, in the case of regression, macro- or microcephaly, seizures, or other clinical indications [12, 13, 39, 42]. In the case of EEG, although children with ASD are at increased risk of seizures, its use is recommended in some settings when there is a clinical concern about seizures, atypical regression, or other neurological symptoms [105]. Finally, with regard to routine metabolic tests for children with ASD, their performance is considered low, and there would not be sufficient grounds to recommend their regular use, although the decision may be based on medical history and family history [64, 106].

Regarding the identification of possible genetic causes, the use of these tests is part of certain recommendations with the aim of ensuring the best possible medical care, for example, to identify the risk of associated disorders such as heart or brain dysfunctions [106]. The frequency of an ASD is important in several genetic conditions, such as Fragile X syndrome, Down syndrome, Rett syndrome, Cornelia de Lange syndrome, tuberous sclerosis, Angelman syndrome, neurofibromatosis type 1, Noonan syndrome, Williams syndrome and 22q11.2 selection syndrome [64, 107].

The AAP suggestions on autism in 2007 indicated karyotype and DNA tests as the most advanced etiological investigations. The latest recommendations from the American College of Medical Genetics and Genomics and the American Academy of Child and Adolescent Psychiatry) suggest a chromosomal microaray (CMA) as the most appropriate initial test for the etiological evaluation of children with ASD and, in some cases, sequencing of the complete exome [12, 13]. The High Authority for Health in France recommends, for its part, that these supplementary examinations be used for cases whose symptoms suggest a concurrent disorder or a differential diagnosis and are carried out and interpreted within the framework of a healthcare organization, such as university hospitals [43]. (For a list of steps to follow in genetic etiological research in people with ASD, see also [31]).

It is important, in all cases, that families are informed about the possible contribution of genetic tests to explain the cause of an ASD or to provide information about a statistical risk but that they do not constitute diagnostic tests for ASD, since this is performed based on the observation of clinical symptoms. It is also important to point out the difficulty of establishing an additional diagnosis of ASD when a person with an identified genetic or sensory disorder presents a behavioral phenotype related to communication difficulties and stereotyped or repetitive behaviors. At the same time, it can be difficult for people with a dual diagnosis to get help for the specific needs of ASD, as these tend to be obscured by the primary diagnosis [108].

Particularities related to the diagnosis of autism in girls

Traditionally, autism has been considered to occur with a frequency of four boys for every girl, but recently, this ratio has been questioned. Indeed, new data suggest that girls have characteristics that diagnostic instruments, developed in essentially male populations, are not capable of capturing [109, 110].

Although some practice guides recognize advances in knowledge about the impact of sex on the clinical presentation of ASD [39, 41, 42], a consensus on phenotypic differences in male and female populations has not yet been established (Ferri et al. 2018), and there are currently no recommendations on how to overcome these barriers to the early diagnosis of girls. However, the results of several recent investigations could provide useful guidelines. For example, data from a systematic review conducted in 2020 suggest that, compared to boys, girls need to have more difficulties in verbal expression or greater severity in behavior problems to be identified and to pass over the diagnostic threshold. The same study suggests that they would be less likely to be referred for a clinical evaluation and that they experience longer wait times

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[111]. On the other hand, there would be several trajectories in the appearance of the first symptoms, with a subgroup that would have an effectively late onset and other subgroups that would have an early onset of symptoms but with subtle characteristics, which would only become evident during adolescence, at a time when social demands are most intense [110]. In addition, the trajectory of the development of social and communication skills in girls would have more subtle deficits and better abilities to adapt to a social environment compared to their male peers [112], which would explain the difficulty of diagnosing autism in adult women and in turn would help to explain that many women with autism are identified with a variety of mental health disorders before reaching a diagnosis of ASD [113].

Co-occurring conditions

Between 10% and 25% of people with autism have a cooccurring disorder [12] including neurological difficulties, particularly epilepsy, and sensory difficulties, such as hearing and vision problems [64].

Health conditions that cause pain must also be taken into account, and people with ASD will not always be able to communicate in a clear way for their environment. Therefore, as previously indicated, the diagnostic process should include careful physical, sensory, and neurological evaluations in a pediatric and neuropediatric setting [41, 43] and, if necessary, with the support of occupational therapists [64].

It is also important to evaluate the impact of other factors, such as sensory overload, atypical eating behaviors, lack of structure in activities, particularly in people with difficulties coping with sudden transitions or changes, difficulties in recognizing their own emotions or others, and the impact of communication deficits that produce frustration for the person [30, 41]. All these difficulties can significantly affect the child's quality of life and clinical management. They can also significantly increase the stress of parents and caregivers and should be taken into account both in the evaluation processes and within an intervention plan.

Discussion

The aim of this work was to review and analyze guidelines for the identification and diagnosis of ASD. Although these guides share an important core of knowledge, they also present certain variability both in the guidelines given for the formation of a team in charge of the diagnosis and in the suggestions for the use of specific instruments. This lack of homogeneity between contents can impact clinical practice globally in several aspects.

First, the variability highlights the potentially determining role of clinical judgment, with the corresponding imperatives in terms of theoretical training and clinical training necessary for its development.

Second, the variability with regard to the aforementioned screening and evaluation instruments suggests the need for some flexibility to choose the instruments most adapted to the person and the context. At the same time, however, caution is required in Latin American contexts, knowing that the validity of an important part of these instruments has not been studied in these countries. Culturally and linguistically appropriate tools are not always available to all users, so the interpretation of the results should be careful and, if necessary, supplemented by supplementary information as appropriate.

A third observation in the face of the heterogeneity of practices is the need to go beyond the evaluation of symptoms. In fact, it is expected, as described in the DSM-5, that health professionals include social, psychological and biological aspects in the formulation of cases. It is therefore important that decision-making actively integrates the material and emotional options available to families in each context.

Finally, the lack of homogeneity between guides corresponds to a situation that has been described as a barrier to the generalization of good practices [114]. For this reason, it is important to underline the existence of a central group of shared knowledge regarding the origins of ASD, the description of the symptoms and their co-occurrences, the main guidelines for their identification and the valid methodologies for your study. This knowledge would be sufficient, at first, to reduce unnecessary variability in the practice of clinical diagnosis, in case management in pediatric settings and in the accompaniment of people with ASD and their families.

Although in certain aspects, the recommendations of the different revised guides may vary in their content and according to the structure of the health systems of the country in which they have been issued, this core knowledge, together with current information on adaptations of good practices to medium- and low-income contexts [115]. They have the vocation to be transferable to a Latin American context, for which it is possible to specify certain basic recommendations:

1. Surveillance through general developmental instruments plus a specific screening questionnaire at 18 and 24 months is suggested, as it can contribute significantly to early detection. Although this carries the risk of identifying false positives, these would generally be cases with other developmental disorders, which also need to be identified.

2. The referral for a diagnostic evaluation of children with positive results in the detection tests should be carried out with the objective of defining an action plan, as well as a follow-up so that the family can understand the objective of each treatment or intervention based on scientific evidence and to be able to participate actively in this plan.

3. Professional training on the different phases of diagnosis, which are anamnesis, interviews with parents, structured and unstructured observation of behaviors and necessary medical examinations, must be guaranteed in pediatric academic contexts.

4. The development of lines of research with local populations should allow responding to immediate problems and sustain the consistent and long-term use of good practices.

5. The study of the impact of cultural and socioeconomic factors, as well as that of the characteristics of health systems, should contribute to predicting specific factors such as waiting times for an evaluation or intervention. These data could also help define, in a transparent way, the eligibility requirements for services in public and private systems.

Strengths and limitations

One of the strengths of this work is the use of a narrative approach, which can contribute to understanding the complexity of the diagnosis of ASD and the nonunique nature of this process. From a methodological point of view, the systematic search that we carried out seeks to provide a transparent point of view on the selection and pragmatic use of the information contained. An important limitation of a review of this type, however, is that it focuses on the analysis of the content of the different guidelines, without being able to account for the way in which their recommendations are implemented in real clinical practice in their different countries. of origin, and above all of its effectiveness in each of these contexts. On the other hand, since it is a review of the current guidelines, they have not been able to analyze the changes over time to be able to conclude on the effectiveness of the long-term recommendations. Finally, although one of the objectives of this work was to make Spanish literature available to the reader, it is scarce, so the review was based on the literature available mostly in English.

Conclusions

ASD has significant identification barriers in Latin America, a fact revealed by the low prevalence rates compared to North America and Europe. All pediatricians should include in their routine control the use of screening questionnaires for children aged 18 and 24 months for early diagnosis of ASD; however, it must be taken into account that most questionnaires have been designed with pediatric populations of patients **of** male sex. **Girls** would have characteristics that diagnostic instruments, developed in essentially male populations, are not capable of capturing.

Abbreviations

ASD: Autism Spectrum Disorder.

Supplementary information

Supplementary materials are not declared.

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Authors' contributions

Paulina Buffle: Conceptualization, Data preservation, Fund acquisition, Research, Resources, Software, Writing - original draft, Writing: review and editing.

Daniela naranjo: Methodology, Formal analysis, Project management, Supervision, Validation, Visualization.

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Availability of data and materials

The data sets generated and/or analyzed during the current study are not publicly available due to the confidentiality of the participants but are available through the corresponding author upon reasonable academic request.

Declarations

Ethics committee approval and consent to participate

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Publication consent

It does not apply to studies that do not publish MRI/CT/Rx images or physical examination photographs.

Conflicts of interest

The authors declare no conflicts of interest.

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