Review article

Recommendations for early diagnosis and intervention in autism spectrum disorders: An Italian–Israeli consensus conference

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Abstract

On April 2013 experts in the field of autism from Italy and Israel convened in Jerusalem to discuss and finalize clinical recommendations for early diagnosis and intervention in Autism Spectrum Disorders (ASDs). In this paper, we summarize the results of this Italian–Israeli consensus conference.

ASDs constitute a class of severe and heterogeneous neurodevelopmental conditions caused by atypical brain development beginning during early prenatal life, reflecting many genetic, neurobiological and environmental influences. The first clinical signs of ASDs begin to be evident in children between 12 and 18 months of age, often after a period of relatively typical postnatal development. Recent longitudinal studies reveal substantial diversity in developmental trajectories through childhood and adolescence. Some intervention approaches have been demonstrated to be effective in improving core symptoms of ASDs, even if the heterogeneity and developmental nature of the disorder make it implausible that only one specific treatment will be best for all children with ASDs. More randomized control trials (RCTs) on early intervention are needed to identify the most effective strategies and provide the most efficient allocation of resources during the critical early intervention time period. Future research should focus on linking biological phenotypes with specific genotypes, thus establishing a foundation for the development of diagnostic screening tools and individualization of treatments.

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1. Introduction

Autism spectrum disorders (ASDs) constitute a class of severe neurodevelopmental conditions caused by atypical brain development beginning during prenatal or early postnatal life and are considered to be life-long conditions, with core symptoms being permanent across the lifespan. In the last years, significant progress has been made in understanding the causes of ASDs and converging links of evidence strongly point towards altered developmentally regulated brain connectivity. Studies of genetic and environmentally modulated epigenetic factors have highlighted the polygenic nature of these conditions, but etiologic causes of ASDs remain elusive in more than 80% of cases; only in 10–20% of the patients neuro-imaging and neurogenetic techniques have allowed to identify a specific medical and genetic syndromes as a cause of ASD.2

These disorders affect today up to one in 88–110 children, being therefore a major public health concern.3–5 The increase in diagnosis rates is probably related to changing diagnostic criteria and to the development and use of new standardized autism-specific diagnostic tools.6 However, taking into account the possibility of modifications in environmental or epigenetic factors, an actual increase of the prevalence of ASDs cannot be completely excluded.

In terms of clinical heterogeneity, the three symptomatological domains of ASDs and the distinction among ASD subtypes as defined by the DSM-IV have often resulted as being not congruent or not useful for studies aimed at examining the underlying structure of the ASD phenotype. Thus, the Working Group for the upcoming version of the DSM 5 has proposed a significant shift in the diagnostic conceptualization of ASDs. Proposed DSM 5 criteria may have in the future an impact on the sensitivity and the specificity of ASD diagnosis.6,7

The wide heterogeneity in the phenotypic presentation, regarding both configuration and severity of behavioral symptoms, reflects numerous genetic and environmental influences.8 No biological diagnostic marker is currently available, and the diagnosis is only based on three symptomatological domains, i.e. impaired social communication, social reciprocity and repetitive/stereotypic behaviors. There are distinct subtypes of autism, which differ in terms of intellectual ability and severity of autistic symptoms, as well as in patterns of cognitive strengths or weaknesses.9 Also the significant heterogeneity in the developmental trajectories can influence the appearance of clinical phenotypes and prospective outcomes of this population.10

The lack of medical tests or biological markers for identifying ASD has led researchers to focus on behavioral phenotypes, in order to detect early signs of autism. Early detection of clinical symptoms at onset and early diagnosis of ASD can improve opportunities for early intervention.11 In recent years an increase in studies on the effectiveness of early intensive behavioral interventions has been reported; however, the current state of evidence is still unclear.12,13

On April 2013 experts in the field of autism from Italy and Israel convened in Jerusalem to discuss and finalize clinical recommendations for early diagnosis and intervention in ASDs. In this paper, we summarize the results of this Italian–Israeli consensus conference.
2. Genetic and epigenetic factors

ASDs are considered the most heritable neurodevelopmental disorder. In fact, genetic factors play a major role in the etiology of autism; however, autism genetics is complex and hard to dissect, due to inter-individual heterogeneity and to many contributing loci and/or multiple gene–environment interactions. Nevertheless, there have been several breakthroughs in our understanding of these heterogeneous disorders. De novo genomic copy number variations (CNVs — gains or losses of genomic material that do not exist in the parents) may explain 7–20% of ASD cases. Recent genome-wide studies show that ASD can be triggered by genetic mutations affecting a very large number of genes, each one accounting for a small fraction of cases. There is also evidence for the contribution of common variations. Recent studies, based on Next Generation Sequencing (NGS), have estimated that mutations in up to 500–1000 different genes may be linked to ASDs, even if the majority of these mutations are very rare. The list of detected genes involved so far in ASD shows an increased proportion of genes associated with synaptic activity, including genes encoding for neurexins and neuroligins (pre- and postsynaptic adhesion molecules that, by bridging the synaptic cleft, regulate trans-synaptic signaling). By interacting with scaffold proteins such as gephyrin and PSD95, these molecules also play a crucial role in stabilizing synaptic receptors in the right place and in maintaining, at network level, an appropriate excitatory/inhibitory (E/I) balance. Such a balance represents a critical condition, which is essential for nearly all brain functions, including representation of sensory information and cognitive processes. An altered E/I balance may lead to developmental disorders and may explain some clinical symptoms of ASDs, like the high incidence of seizures or the altered sensitivity to auditory or visual stimuli. Alterations of the balance of glutamate and γ-aminobutyric acid (GABA) at synaptic level, and altered structural organizations of the GABAergic synapses have been observed as well. Interestingly, early generated GABAergic interneurons are instrumental for the construction of neuronal circuits. They exert a powerful control on network excitability and are responsible for the oscillatory behavior crucial for information processing.

It is worth mentioning that the onset of ASDs coincides with the period of maximal synaptogenesis and experience-dependent synaptic plasticity. Multiple genetic risk variants associated with ASDs encode primarily for scaffolding proteins and cell adhesion molecules, which play a crucial role in synaptogenesis and neuronal differentiation and plasticity. Likewise, animal models of monogenic diseases associated with autism, such as Fragile X or Rett syndromes, show specific alterations of synaptic plasticity. Similar defects have been observed also in animal models for non-syndromic autism. Even if no genetic variant could be currently defined as the “cause” of ASD, these data might point to a disturbed synaptogenesis as one of the key shortcomings of ASDs.

In addition, genes involved in transcription regulation during brain development, specifically chromatin regulators, play a prominent role in ASDs. This data highlights how genes are functionally related as part of gene co-expression regulatory networks, which include also epigenetic modifications. Larger genetic databases will be needed to detect such complex biomarkers, that is why the regular collection of genetic information in each person with ASD should be encouraged. In fact, genetic or co-morbid medical conditions in children with ASDs can correlate negatively with long term outcome and with the effectiveness of treatment. In this view, it is important to underline the importance of obtaining a comprehensive medical work-up for young children with ASDs, as summarized in Table 1. The recommended evaluation for ASD includes also chromosomal microarray analysis (CMA) and testing for Fragile X syndrome, but does not include sequencing of specific genes/panel of genes or the whole genome/exome, as in the case of complex disorders like ASDs, widespread genetic testing would not only be expensive and time-consuming, but also generally inappropriate due to its etiological complexity.

Many genetic questions, such as the role of epigenetics in ASDs, are still unanswered. Whereas ASDs have a significant genetic basis, with an inheritability of 60–90%, genetic factors alone do not provide a full explanation for the increased prevalence: non-heritable environmental factors might play a role as well.

Table 1 – Practical recommendations for medical work-up in ASDs.

<table>
<thead>
<tr>
<th>Practical recommendations for medical work-up in ASDs:</th>
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<tbody>
<tr>
<td>Ensure an accurate diagnosis of ASDs</td>
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<tr>
<td>Discuss test options with family before proceeding with any investigations</td>
</tr>
<tr>
<td>Define an individualized medical work-up plan based on the unique history and clinical features of the given patient (e.g., dysmorphic features, gastrointestinal disorders, motor delay, seizures, developmental regression, lack of active language, macrocephaly)</td>
</tr>
<tr>
<td>Recognize the expanded phenotype of syndromic and metabolic disorders associated with ASDs</td>
</tr>
<tr>
<td>Consider sleep EEG in all children with ASDs and a history of regression</td>
</tr>
</tbody>
</table>

**Genetic evaluation:** DNA microarray analysis proposed as a first tier evaluation of children with ASDs

- NGS (Next Generation Sequencing) technique and exome sequences have great potential for the identification of the novo mutations in ASDs children.
- Fragile X (if cognitive impairment is present)
- MECP2 in females with regression
- PTEN for head circumference >2.5 SD of mean (severe macrocephaly)
- SHANK3 for autism with severe language and social deficits

**Metabolic screening:** To be considered in the presence of suggestive clinical findings as: autonomic regression, lethargy, cyclic vomiting, early onset seizures, dysmorphic features, hyper-hypotonia, self-mutilations, muscle weakness, immune deficiency or haemolytic anaemia

Genetic or co-morbid medical conditions in children with ASDs can correlate negatively with long term outcome and with the effectiveness of treatments. It is important to obtain a comprehensive medical work-up for young children with ASDs. These evaluations will enable better planning of individualized and tailored interventions.
At present, no individual factor in the neonatal and perinatal periods has been consistently validated as a risk factor for autism. However, some pre- and perinatal events that have been associated with ASDs might be possible causes of ASDs.23

1. Among the possible environmental risk factors, advanced maternal and paternal ages, intra-uterine infections, exposure to toxins and medication use (mostly for epilepsy and psychiatric conditions), preterm birth, low birth weight, hypoxia-related events, use of assisted reproductive technologies, and male gender have been described.24 While ASDs are mainly genetic in origin, these birth and familial risk factors may represent a “second-hit” phenomenon that affects embryonic and/or fetal brain development and may modulate an already existing genetic susceptibility, contributing to the variable manifestations of ASDs. Indeed, in ASDs associated with prematurity or low birth weight — contrary to ASD without these factors — only adaptive skills and not autism severity were noticeably affected.25,26 In addition, females with ASD experience more complex clinical and neurological manifestations and present more often with a history of social regression than males, suggesting different etiologies and more extensive brain dysfunction (Ben-Itzchak E, Ben-Shachar S, Zachor DA. Specific neurological phenotypes in autism spectrum disorders are associated with sex representation. In press).

3. Brain abnormalities and neuro-imaging

The heterogeneity of etiologies of ASDs is limiting causal research and its translation into clinical practice; experimental or observational studies often include sample of biologically heterogeneous cases, hampering the full understanding of genetic or molecular endophenotypes.27 The clinical complexity of ASDs, due also to the extensive range of interactions between multiple genetic loci and epigenetic factors, explains the increasing difficulties encountered in identifying the primary cause of these neurobiological aberrations.

Nevertheless, studies of genetic and environmental epigenetic factors are beginning to provide some clues to clarify the complexities of autism pathogenesis, which has been associated with altered functional and structural connectivity patterns in several brain regions that occur early in life.1 In fact, functional and structural neuroimaging studies consistently show patterns of disrupted white matter integrity in toddlers, children, and adults with ASDs.28,29 Such observations might lead, in future, to identify early biomarkers that will enhance a more straightforward diagnosis of the disorder and, at the same time, foster the detection of novel treatment targets.

Furthermore, several molecular pathways potentially involved in the disruption of neurodevelopmental trajectories during intrauterine or postnatal brain development may be associated with abnormal developmental processes. In terms of brain anatomy, ASDs individuals compared to neurotypical subjects, show differences in brain growth trajectories of grey and/or white matter volumes and head circumferences.30 It has been consistently observed that a subgroup of children with ASDs presents an accelerated brain growth in early childhood, which concerns the overall brain and might be partially linked to abnormal accelerated myelination.31 On the contrary, in adolescence and adulthood, after a period of abnormal sluggish or arrested brain growth, no general brain differences are observed, but only spatially distributed ones, like, among others, alterations of the corpus callosum, splenium, left anterior thalamic radiation, cerebellum, amygdale—hypocampal complex and several other intra-hemispheric tracts.32 These distorted developmental brain trajectories may lead to neuroanatomical differences not only in distinct regions, but in complex neural systems as well, and these abnormalities may mediate some particular traits of ASDs, as altered social interactions, impairment in emotion, or communication. According to these findings, ASDs appear to be mainly a disorder of distributed large-scale cortical networks rather than of specific brain areas. It has been suggested that disturbed, abnormal and disorganized inter- and intra-cortical connections are one of the core issues in autism, resulting in poorly synchronized neural networks, which in turn lead to abnormal cognitive and neurological functioning.33 The timing of brain enlargement may also be a relevant detail for the prospective studies of the onset of ASDs. The temporal relationship between the onset of both autistic behavior and brain overgrowth in the latter part of the first year of life suggests that the increased rate of brain growth may be linked to the onset of autistic symptoms, perhaps through a physical disruption of neural circuitry.33

The advance in neuro-imaging techniques has played an important role in suggesting abnormal functional brain organization in ASDs. Functional MRI (fMRI) studies have showed alterations of the functional anatomy of different cortical networks, both regarding the size and the areas included in the networks.34 Together with longitudinal studies showing altered white matter maturation curves, these data led to the development of the so-called underconnectivity theory of autism, which points to the interaction of multiple partial cortico-cortical and cortico-striatal (the major input station of the basal ganglia) disconnections as one of the main underlying pathological correlates of autistic disorders.35 Abnormalities of both functional and structural connectivity have been consistently observed.

Using diffusion tensor imaging (DTI), abnormal integrity of the white matter has been reported in subjects with autism in several brain networks including the short and long association fibers in the frontal lobes, temporal regions, regions near the genu of the corpus callosum, white matter underlying the anterior cingulate cortex and the left orbitofrontal cortex network.35,36 Few diffusion studies reported results in young children with autism. These studies described an opposite trend of increased FA values, in several brain regions compared to reduced FA values that were reported at older ages.37–39 It has been proposed that such abnormal white matter integrity in young children with autism may adversely affect connectivity between different brain regions and may be linked to some of the behavioral and language impairments apparent in autism.39 Detection of brain abnormalities at this young age holds promise for early diagnosis and prognosis of
children with autism. In this view, the participation of people with ASDs in such imaging studies should be encouraged.

Functional neuroimaging studies indicate that also age may have a significant effect on white matter differences in ASDs, possibly relating to the timing on white matter disruption in the autistic brain. Recent findings led to hypothesize that the last part of the first year of life could be a crucial time for anatomical changes in the brain (resulting then in symptoms onset) of children who will later be diagnosed with ASDs. Preliminary findings of a DTI study in high-risk infant siblings suggest a distinct and pervasive course of white matter fiber tract development that characterizes high-risk infants going on to develop autistic symptoms. These altered developmental trajectories begin before the onset of clinical symptoms, suggesting that the core behavioral features of ASDs may arise from an altered neurobiological foundation and that differences in structural organization prior to a period of experience-dependent development may decrease neural plasticity and connectivity through limitations on environmental inputs.

Findings of differences in choline metabolism as well as partial responses to pharmacological treatments (Atypical neuroleptics and Methylphenidate) that modulate serotonin (SSRIs), dopamine, and norepinephrine, led to view autism also as a neurotransmitter disorder. The search for a metabolic abnormality in autism using MR spectroscopy technique led to the discovery of Creatine Deficiency Syndromes, in which autism might be one of the presenting symptomatologies.

Other studies have suggested that ASDs may be related to disorders of the synapse structure, to development stabilization, and to transmission. Abnormal synaptic function, as described above, may lead to altered connectivity, hyperexcitable or less reliable neurons (“noisy neurons”), as well as to differences in neural plasticity and adaptation that, by using neurophysiological studies, may be detected in early infancy. For these reasons, autism has been sometimes described also as a disorder of neural synchronization. However, it is unknown how early in development synchronization abnormalities emerge and whether they are related to the development of early autistic behavioral symptoms. Recently, disrupted synchronization in the spontaneous cortical activity of naturally sleeping toddlers with autism has been reported; such disruptions were not present in toddlers with language delay (without autism) or with typical development. Toddlers with autism exhibited significantly weaker interhemispheric synchronization (i.e. weak “functional connectivity” across the two hemispheres) in putative language areas. Synchronization strength correlated positively with verbal ability and negatively with autism severity, enabling to identify up to 72% of autistic toddlers with an accuracy of 84%. Disrupted cortical synchronization, therefore, appears to be an important characteristic of autism neurophysiology at very early stages of autism development. Another promising research direction includes assessment of trial-by-trial neural response reliability, which is a measure of neural “noise”. A recent study has reported that low response reliability (poor consistency across trials) is apparent across the visual, auditory, and somatosensory systems of adults with autism. Future research will determine whether such poor reliability (increased “neural noise”) appears during early autism development. Abnormalities in the general neural function may become a means to identify autism at early stages using non-invasive imaging techniques.

### 4. Early signs and follow-up surveillance

The clinical diagnosis of autism is generally performed in children between 18 and 30 months of age, but autistic features, such as limitations in joint attention, eye contact, reciprocal smiling, imitation, response to name, gestures (i.e.

<table>
<thead>
<tr>
<th>Age</th>
<th>Social interaction</th>
<th>Communication</th>
<th>Stereotyped behaviors</th>
<th>Skills development and behavior characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–15 months</td>
<td>Poor eye contact; Deficit of social smiling; Negative affect.</td>
<td>Poor vocalizations.</td>
<td>Lack of reactivity.</td>
<td>Delay in fine motor development; Concerns about vision.</td>
</tr>
<tr>
<td>15–18 months</td>
<td>Failure to respond to name; Deficit of visual attention; Failure to show things to others and to share interest; Negative affect.</td>
<td>Delay of expressive and receptive language; Absence/poor pointing.</td>
<td>Repetitive patterns of play; Atypical visual attention and object exploration.</td>
<td>Concerns about hearing; Differences in feeding behavior.</td>
</tr>
<tr>
<td>18–24 months</td>
<td>Failure in imitation; Absence of interest for others children; Poor reactivity to others’ emotions; Limited range of facial expressions.</td>
<td>Delay of expressive/receptive language; No coordination between eye contact and verbal communication; Echolalia.</td>
<td>Restricted interests and repetitive activities; Motor stereotypies.</td>
<td>Temperamental traits; Feeding difficulties and fads; Bowel habit and stool characteristics.</td>
</tr>
</tbody>
</table>

The table depicts precursors, early signs, and other developmental differences reported in the first year of development among children who will later developed Autism Spectrum Disorders (ASDs). It is important to recognize these early predictors of ASDs and refer immediately to autism specialists for diagnosis.
pointing), and pretend and imaginative play skills begin to be evident already in children between 12 and 18 months of age, often after a period of relatively typical postnatal development.47 Table 2 illustrates the first morbid manifestations more often detected during the first months of life and over the following 12 months; most of the infants who were later diagnosed with ASD demonstrated declining trajectories of social communication behavior and loss of skills, as, e.g., rapid decline in eye contact, social smiling, and examiner-rated social responsiveness.48 As recommended by different Practice Parameters, and as indicated in Table 3, an appropriate and timely ASD diagnosis requires two levels of investigation: a routine developmental surveillance, and a more appropriate and timely ASD diagnosis requires two levels of investigation: a routine developmental surveillance, and a more specialized center for a more specific diagnostic management. Pedi-

| Table 3 – Practical recommendations for ASDs screening and clinical assessment. |
|---------------------------------|--------------------------------|-----------------------------------------------------------------|
| Level 1: Screening tools for ASDs, which can be used by general pediatricians. |
| CHAT: Checklist for Autism in Toddlers (Baron Cohen, 1992) A checklist for autism in toddlers |
| Age: 18–24 months |
| Test includes: Parent interview or questionnaire and interactive assessment of the child |
| M-CHAT: Modified Checklist for Autism in Toddlers A questionnaire completed by parents. If relevant items are positive, further assessment by the pediatrician |
| Age: 16–48 m |
| PDDST-II- A broadband screen at the 1-year check-up to detect cases of autism spectrum disorders, language delay and developmental delay |
| Pervasive developmental disorder screening test for primary care screeners |
| Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist CSBS (Pierce et al., 2011) |
| Level 2: Abnormalities at Level 1 call for assessment at specialized developmental clinics. |
| SCQ: Social-communication questionnaire A 40 (yes/no) questions based on items from the Autism Diagnostic interview (ADI). |
| Age: >4 years |
| SRS: social responsiveness scale |
| Level 3: “Gold standard tests” – used in ASDs special clinics |
| ADI-R – Autism Diagnostic Interview-Revised A semi-structured interview administered to parents, designed to make a diagnosis of autism according to DSM-IV criteria (Le Couteur et al., 2003). |
| ADOS – Autism Diagnostic Observation Schedule A semi-structured, interactive schedule designed to assess social and communicative functioning (Lord et al., 1999). |

5. Developmental trajectories

Developmental trajectories may help understanding whether different etiologies are associated with different phenotypic expressions. Recent longitudinal studies reveal substantial diversity in trajectories through childhood and adolescence, as well as changes in autism symptoms over time.54 Identifying the details of such changes could theoretically help in the search of biomarkers of ASDs, which could complement the traditional behavioral diagnosis and contribute to predict treatment responses. However, the development of reliable biologic diagnostic tests has so far been limited by the complexity of the disorder.55 Supposed biomarkers will probably have to be complex, looking both at biology and genetics, rather than to a single feature.

Associations between developmental trajectories and language and motor delay, altered sensory patterns, or lower level of cognitive functioning have been observed as well.51 Also socioeconomic factors have been correlated with trajectories outcome.56 Many developmental studies in the first 3 years of life are based on high risk infants, like siblings of people with ASDs, where recurrence rates are about 19%. Three quarters of these siblings affected by ASDs fail to acquire normative developmental skills at 6–36 months. Espe-

Social and communicative skills, verbal and non–verbal mental age – measured with standardized instruments supporting clinical judgment – can predict developmental

From a theoretical perspective, constraints or growth in one developmental domain may influence change across other important domains. For example, the additional burden of language impairment in young children with ASDs may lead to further lags in their social understanding.53

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Social and communicative skills, verbal and non–verbal mental age – measured with standardized instruments supporting clinical judgment – can predict developmental
trajecories from 18 to 36 months.\textsuperscript{57} The observation of children over a wide range of ages (from childhood to adolescence) shows that many of them experienced substantial development heterogeneity, especially in the social dimension. The most rapid development occurred before age 6, and several of the trajectories tended to flatten out after that, while repetitive behavior trajectories remained relatively stable over time. The coexistence of intellectual disabilities, as well as socioeconomic factors, has been also correlated with different developmental trajectories.\textsuperscript{52}

It is worthwhile to mention that studies on developmental trajectories have also revealed the existence of a particular category of children, sometimes identified as “bloomers” or “accelerated”, that quickly improved over time: it may represent a neurobiological and genetically protective category.\textsuperscript{56}

Researchers have emphasized the need for more knowledge about developmental trajectories, especially about early symptomatology, arguing that it would improve intervention and care.

6. Early intervention

The complexity of ASDs is reflected also in the lack of effective treatments. Currently, autism is a disorder that results in lifelong disability in the majority of individuals and no therapy has been proven to completely reverse the core symptoms of autism. Nevertheless, intensive and early interventions are able to improve some aspects of the disorder.\textsuperscript{58,59} Research studies have shown that greater intensity of treatment, longer durations, and early age at intervention onset led to better outcomes. Some intervention approaches, mostly based on behavioral and developmental principles, have been demonstrated to be effective in improving ASDs symptoms, as well as cognitive and adaptive skills. The theoretical foundation for early treatment is based on the notion of early brain plasticity, with research showing that the structure and connectivity of the brain are particularly “open to change” during early childhood.\textsuperscript{57} Early intervention can also provide the stimulation for the development of efficient neuronal circuits, which are probably less robust in ASDs, and it has been associated with normalized patterns of brain activity and improvements in social behavior.\textsuperscript{37,47}

6.1. Non-pharmacological treatments

With regard to non-pharmacological treatment research, it should be highlighted that the strength of evidence of efficacy varies among the different studies from insufficient to moderate.\textsuperscript{58} Such limited evidence arises from methodological weaknesses of the majority of the studies. Only few studies were clinical trials, most of them were based on small samples, the populations were heterogeneous, the interventions were operated in assorted intensity and time, the objectives of the studies were different, and there was a lack in long-term and follow-up studies.\textsuperscript{58} Furthermore, there is also a shortage of studies that compare different interventions. In this context, there is a huge need to design and perform methodologically sound long-term prospective studies. More RCTs on early intervention are needed to identify the most effective strategies to improve global functioning of children and reduce symptoms severity.\textsuperscript{57} This is the only way to make sure that a specific treatment works and that it really promotes the child’s health and development.

In any case, the heterogeneity and developmental nature of the disorder make it doubtful that one specific treatment will be best for all children with ASDs. Thus, researches for individualized treatments are important in order to decrease the outcome variability and provide the most efficient allocation of resources during the critical early intervention time period. Such research requires an understanding of some specific factors, such as the pre-treatment predictors, associated with differential response of intervention and the evaluation of any clinical/medical condition that can affect the outcome.\textsuperscript{58} It is crucial to identify clinical characteristics associated with a more positive outcome. For instance, in terms of predictors of outcome at first diagnosis, children with less symptom severity, who have higher cognitive ability and better receptive language skills, and/or whose mothers do not belong to ethnic minorities might respond better to treatment.\textsuperscript{53,59,60} However, at present, the available information on predictors of outcomes is still inconclusive. Future research should focus on the prognostic value of proximal variables that are theoretically relevant for treatment response; the selection of the putative predictors should be informed by the knowledge of the learning processes upon which the educational procedures of a specific program are based. For all these reasons, it is advisable to integrate different but appropriate strategies, proved by research to be effective, by considering more than one intervention for teaching multiple skill areas and by varying the proportion of time spent using each one, taking into account also the characteristics of the child and the family. On the other hand, it is also important to avoid “eclectic” approaches, which are often inconsistent and mix together effective and ineffective procedures.\textsuperscript{51,63} In any case,

<table>
<thead>
<tr>
<th>Table 4 – Practical recommendations for early intervention in ASDs.</th>
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<tbody>
<tr>
<td>Begin an early, intensive and comprehensive intervention immediately after the diagnosis</td>
</tr>
<tr>
<td>Individualized and tailored intervention according to the child’s developmental trajectory</td>
</tr>
<tr>
<td>Collaborate with families to develop a comprehensive multimodal treatment plan encompassing support and educational for the parents</td>
</tr>
<tr>
<td>Individualized intervention targeted to each child’s needs</td>
</tr>
<tr>
<td>Intervention for ASDs should include behavioral principles as part of the treatment plan</td>
</tr>
<tr>
<td>Consider more than one intervention strategy for teaching multiple skill areas</td>
</tr>
<tr>
<td>Depending on local service settings and program availability, implement EBI principles and add the most effective evidenced-based strategies for improving global functioning and reducing symptoms severity</td>
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</table>

Treatment individualization in ASDs is important to minimize outcome variability and to provide the most efficient allocation of resources during the critical early intervention time period. This table summarizes basic practical recommendations for the development of a more effective and individualized treatment plan.
it should always be stressed that an optimal outcome of treatments, even if rare, is not impossible, particularly with more intense and longer interventions.58 Table 4 summarizes these basic practical recommendations to help develop more effective and individualized treatment plans.

7. Intervention models in ASDs

Multiple research articles, despite the limitations mentioned before, document some effectiveness of different behavioral methods for teaching a variety of skills.63-65 Some of the most frequently used methods are outlined here.

7.1. Developmental, individual difference, relationship-based model of intervention (DIR)

The developmental approach-teaching goals are derived from an assessment of children’s developmental skills by an interdisciplinary team, yielding an individualized developmental profile on the child’s cognitive, communicative, social, motor, and self-help skills. The focus is on imitation, play and social reciprocity in natural environments.46

Individualized interventions help the child to build successively higher levels of social, emotional, and intellectual capacities through affect-based interactions. Practice based evidence on the DIR model has validated the conceptualization of the model.67 Recent studies using RCT methodology have shown better language and cognitive outcomes, as well as greater parent satisfaction.58-70 Other studies, using developmental models, also show significant gains when developmental criteria are applied to intervention.60,71

7.2. The treatment and education of autistic and related communication handicapped children (TEACCH)

TEACCH emphasizes two basic principles: structuring the environment to promote skill acquisition and facilitating independence at all levels of functioning. The underlying premise for structured teaching is to modify the environment in order to meet the needs of individuals with ASD. Four main components are related to this process, i.e. physical organization, visual schedules, work systems, and task organization.72 TEACCH has been implemented in many different countries and adapted to different situations (home-based, mainstream schools, special schools, residential centers). Some studies indicate that TEACCH could be recommended particularly for low-functioning subjects with ASDs.73

7.3. Applied behavioral analysis (ABA)

ABA is an educational-behavioral intervention, based on the principles of behavior, using systematic, step by step teaching, prompts and useful reinforcements.74 Children are taught skills including attention, basic discrimination, language and communication, daily living, socialization, play, fine and gross motor control and pre-academics.1,71,75,76 This program is comprehensive and uses various strategies to promote the child’s engagement and experience with the social environment. The strategies include discrete trial training (DTT) and naturalistic behavioral approaches (incidental teaching, natural language paradigm, pivotal response training) that are planned according to the child’s strengths and difficulties. Behavioral interventions are effective for improving language, cognitive abilities, adaptive behavior, and social skills, and reducing anxiety and aggression.12,65 ABA programs have been identified by some authors as the treatment of choice.75

7.4. The early start denver model (ESDM)

ESDM is a comprehensive early intervention program designed to target the core deficits seen in toddlers and preschoolers with autism. The ESDM has an interactive, communication and relationship-based framework that fosters active experiential learning by supporting the child’s spontaneity and initiative.71 This early intervention program integrates a relationship-focused developmental model with the teaching practices of ABA. Its core features include naturalistic applied behavioral analytic strategies, sensitive to normal developmental sequence, deep parental involvement, focus on interpersonal exchange and positive affect, shared engagement with joint activities, and language and communication taught inside a positive affect-based relationship.11,12

7.5. Pharmacological treatments

To date, no pharmacological treatment has been proven to either cure ASDs or to improve its core symptoms. This is due to the fact that research is limited by a lack of valid and reliable cellular assays and animal models, and by the clinical heterogeneity of this population. Nonetheless, the wide range of maladaptive behaviors, characterized by self-injurious, aggressive, and hyperactivity/inattention symptoms, as well as by repetitive behaviors and stereotypes, can considerably interfere with overall functioning and with the efficacy of the above mentioned interventions. Moreover, the co-occurrence of medical comorbidities (as seizures, sleep disorders, or gastrointestinal disturbances) causes a significant burden on the affected children/adolescents and their families. For these reasons, several classes of medications can be used to target specific symptoms and can be combined as part of an integrative treatment plan.77,78

8. Other areas of intervention in the clinical management of ASDs

8.1. Use of functional analysis

Functional Analysis can provide educators with reliable information, enabling the detection of frequent patterns and understanding the reasons for specific behaviors. Functional analytic conclusion is based on data collection that helps identify the context variables that precede the behavior (antecedents) and consequences related to the challenged behavior. Such an intervention may be applied in various contexts79 and integrated in specific educational programs.80
Abnormalities in interpersonal relations are considered a defining characteristic of ASDs. Friendship is a direct reflection of the child’s capacity for interpersonal relationships, and for this reason, both the formation and the understanding of friendship in children with ASDs are considered a major theoretical challenge. Empirical findings do show that development of friendship is in the capacity of some children with ASDs most likely with high functioning ASDs. Social interventions should go beyond teaching social skills, to help teach children the skills necessary to form friendships with their peers. The enhancement of friendship in early intervention may possibly lead to reduced rates of comorbid affective disorders such as depression and anxiety at older ages.

### 8.3. Social skills training (SST)

Recent developments SST interventions have shown a shift from focusing on the enhancement of specific social behaviors — such as listening, eye contact, conversational skills, or gestures — to a multidimensional perception of social functioning. This multidimensional perception encompasses the child’s capacity to integrate behavioral skills (e.g., social interaction), cognitive skills (e.g., accurate processing of information, perspective taking, social understanding), and affective skills (e.g., emotional regulation, knowledge, and recognition) in order to adapt flexibly to diverse social contexts and demands. Social interventions for children with ASD are also shifting from skills-oriented SST programs based mainly on social behaviors to more comprehensive, holistic interventions based on modifications of classic cognitive-behavioral treatment (CBT) models, to help these children engage in more effective interactions with peers as well as to enhance their socio-cognitive understanding of social constructs and processes and reducing their anxiety. Despite their potential significance, these models have not been tested so far for preschoolers with ASDs. It should be also mentioned that the limitation of CBT is that it requires cognitive capabilities in order to gain benefits from the treatment, thus it may be limited to the higher functioning children with ASD.

### 8.4. Feeding problems in ASD

The prevalence of feeding difficulties in children with ASD is estimated to be as high as 90%, with approximately 70% having food selectivity. Risks are associated with poor weight gain, malnutrition and dehydration, as well as learning and behavioral problems, adult disease and potential damage to parent–child relationship. Assessment of feeding difficulties in children with ASDs is complex and should be conducted by a multidisciplinary team. Treatment should be tailored to the individual. Some therapy adaptations, like the use of visual supports, the attention to sensory sensitivities, and gradual progression when introducing new foods, have shown to be beneficial. Further research is needed to evaluate the effects of selective eating, early intervention and type of treatment on later development.

### 9. Future directions

A major goal of the current interdisciplinary researches is to understand specific and non-specific factors that influence variability both in the relative risk of developing autism, and in the responsiveness to treatments. The clinical heterogeneity of ASDs might be reduced when more homogeneous subgroups, based on a specific genotype or epigenetic mechanisms, are extracted from the overall genetically heterogeneous ASD population. The existence of specific ASD genotypes also implies that these could be rescued by specific, targeted molecular treatments.

In the future, animal models of monogenic diseases associated with autism, such as Fragile X syndrome, Rett syndrome, or Tuberous Sclerosis, may provide a better understanding of the pathogenetic mechanisms underlying ASDs and could help in the development of more effective treatment strategies.

A future goal will be to better understand whether very early intervention may result not only in significant improvements in behavior — including reduced autism symptoms and increased cognitive, language, and social abilities — but also in significant changes in brain function and organization related to functional recovery. This will help to identify the neurobiological mechanisms responsible for effective outcome following intervention and might, therefore, suggest the way to reduce or even prevent the manifestations of the full syndrome.

With a better understanding of the biochemical alterations of ASDs it will be possible to detect early biomarkers for the diagnosis of ASDs, to improve our knowledge and ability to develop pharmacological therapies, to elaborate more definite interventions on the basis of the different clinical phenotypes, and thus bridge the gap between scientific research and clinical applications.

### Appendix. List of participants

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