6-year surveillance 2016 – Autism spectrum disorder in under 19s: recognition, referral and diagnosis (2011) NICE guideline CG128

Appendix A.1: summary of new evidence

Recognition

Local pathway for recognition, referral and diagnostic assessment of possible autism

Recognising children and young people with possible autism

Referring children and young people to the autism team

128 – 01 **a) What are the signs and symptoms that should prompt a healthcare professional or other professional in any context to think of autism?**

Recommendations derived from this question

1.1.1 A local autism multi-agency strategy group should be set up, with managerial, commissioner and clinical representation from child health and mental health services, education, social care, parent and carer service users, and the voluntary sector.

1.1.2 The local autism strategy group should appoint a lead professional to be responsible for the local autism pathway for recognition, referral and diagnosis of children and young people. The aims of the group should include:

- improving early recognition of autism by raising awareness of the signs and symptoms of autism through multi-agency training (see tables 1–3 in appendix C)
- making sure the relevant professionals (healthcare, social care, education and voluntary sector) are aware of the local autism pathway and how to access diagnostic services
- supporting the smooth transition to adult services for young people going through the diagnostic pathway
- ensuring data collection and audit of the pathway takes place.

1.1.8 Provide a single point of referral for access to the autism team.

1.2.1 Consider the possibility of autism if there are concerns about development or behaviour, but be aware that there may be other explanations for individual signs and symptoms.

1.2.2 Always take parents' or carers' concerns and, if appropriate, the child's or young person's concerns, about behaviour or development seriously, even if these are not shared by others.

1.2.3 When considering the possibility of autism and whether to refer a child or young person to the autism team, be critical about your professional competence and seek advice from a colleague if in doubt about the next step.

1.2.4 To help identify the signs and symptoms of possible autism, use tables 1–3 (see appendix C). Do not rule out autism if the exact features described in the tables are not evident; they should be used for guidance, but do not include all possible manifestations of autism.

1.2.5 When considering the possibility of autism, be aware that:

- signs and symptoms should be seen in the context of the child's or young person's overall development
- signs and symptoms will not always have been recognised by parents, carers, children or young people themselves or by other professionals

- when older children or young people present for the first time with possible autism, signs or symptoms may have previously been masked by the child or young person's coping mechanisms and/or a supportive environment
- it is necessary to take account of cultural variation, but do not assume that language delay is accounted for because English is not the family's first language or by early hearing difficulties
- autism may be missed in children or young people with an intellectual disability
- autism may be missed in children or young people who are verbally able
- autism may be under-diagnosed in girls
- important information about early development may not be readily available for some children and young people, for example looked-after children and those in the criminal justice system
- signs and symptoms may not be accounted for by disruptive home experiences or parental or carer mental or physical illness.

1.2.6 When considering the possibility of autism, ask about the child or young person's use and understanding of their first language.

1.2.7 Do not rule out autism because of:

- good eye contact, smiling and showing affection to family members
- reported pretend play or normal language milestones
- difficulties appearing to resolve after a needs-based intervention (such as a supportive structured learning environment)
- a previous assessment that concluded that there was no autism, if new information becomes available.

1.2.8 Discuss developmental or behavioural concerns about a child or young person with parents or carers, and the child or young person themselves if appropriate. Discuss sensitively the possible causes, which may include autism, emphasising that there may be many explanations for the child's or young person's behaviour.

1.2.9 Be aware that if parents or carers or the child or young person themselves have not suspected a developmental or behavioural condition, raising the possibility may cause distress, and that:

- it may take time for them to come to terms with the concern
- they may not share the concern.

1.2.10 Take time to listen to parents or carers and, if appropriate, the child or young person, to discuss concerns and agree any actions to follow including referral.

1.3.1 Refer children younger than 3 years to the autism team if there is regression in language or social skills.

1.3.2 Refer first to a paediatrician or paediatric neurologist (who can refer to the autism team if necessary) children and young people:

- older than 3 years with regression in language
- of any age with regression in motor skills.

1.3.3 Consider referring children and young people to the autism team if you are concerned about possible autism on the basis of reported or observed signs and/or symptoms (see tables 1–3 in appendix C). Take account of:

- the severity and duration of the signs and/or symptoms
- the extent to which the signs and/or symptoms are present across different settings (for example, home and school)
- the impact of the signs and/or symptoms on the child or young person and on their family

- the level of parental or carer concern and, if appropriate, the concerns of the child or young person
- factors associated with an increased prevalence of autism (see box 1)
- the likelihood of an alternative diagnosis.

Box 1 Factors associated with an increased prevalence of autism

- A sibling with autism
- Birth defects associated with central nervous system malformation and/or dysfunction, including cerebral palsy
- Gestational age less than 35 weeks
- Parental schizophrenia-like psychosis or affective disorder
- Maternal use of sodium valproate in pregnancy
- Intellectual disability
- Neonatal encephalopathy or epileptic encephalopathy, including infantile spasms
- Chromosomal disorders such as Down's syndrome
- Genetic disorders such as fragile X
- Muscular dystrophy
- Neurofibromatosis
- Tuberous sclerosis

1.3.4 If you have concerns about development or behaviour but are not sure whether the signs and/or symptoms suggest autism, consider:

- consulting a member of the autism team who can provide advice to help you decide if a referral to the autism team is necessary
- referring to another service. That service can then refer to the autism team if necessary.

1.3.5 Be aware that tools to identify children and young people with an increased likelihood of autism may be useful in gathering information about signs and symptoms of autism in a structured way but are not essential and should not be used to make or rule out a diagnosis of autism. Also be aware that:

- a positive score on tools to identify an increased likelihood of autism may support a decision to refer but can also be for reasons other than autism
- a negative score does not rule out autism.

1.3.6 When referring children and young people to the autism team, include in the referral letter the following information:

- reported information from parents, carers and professionals about signs and/or symptoms of concern
- your own observations of the signs and/or symptoms.

1.3.7 When referring children and young people to the autism team, include in the referral letter the following information, if available:

- antenatal and perinatal history
- developmental milestones
- factors associated with an increased prevalence of autism (see box 1)
- relevant medical history and investigations
- information from previous assessments.

1.3.8 Explain to parents or carers and, if appropriate, the child or young person, what will happen on referral to the autism team or another service.

1.3.9 If you do not think concerns are sufficient to prompt a referral, consider a period of watchful waiting. If you remain concerned about autism, reconsider your referral decision.

1.3.10 If the parents or carers or if appropriate, the child or young person, prefer not to be referred to the autism team, consider a period of watchful waiting. If you remain concerned about autism, reconsider referral.

1.3.11 If a concern about possible autism has been raised but there are no signs, symptoms or other reasons to suspect autism, use professional judgment to decide what to do next.

Surveillance decision

This review question should not be updated.

2-year evidence update summary

Six studies were found reporting on signs and symptoms of autism:

A retrospective analysis of data from a cohort study reported early predictors of later autism related to developmental differences compared to the general population:[1]

- At age 6 months, differences in fine motor skills and social skills and communication, and concerns about vision.
- At age 15 months, differences in hearing, vocabulary and understanding words, and in feeding difficulties and feeding habits.
- At age 18 months, differences in listening and responding to sounds, play and imitation, health concerns and repetitive and unusual behaviours.
- At age 24 months, differences in temperamental traits, bowel habit and stool characteristics.
- At age 30 months, differences in crying and tempers.

Two studies compared differences in behavioural features of autism spectrum disorders (ASDs) between boys and girls:

- Girls had less repetitive stereotyped behaviour, fine-motor impairment and lower hyperactivity and inattention than boys as well as higher level of emotional problems and prosocial behaviour (study type not specified in abstract)[2].
- Girls were less likely than boys to show aggressive behaviour or hyperactivity or short attention span but were more likely to have seizures or seizure-like behaviour (study type not specified in abstract)[3].

A study reported that first concerns about autism occurred more than 2 months later for children who had regression or plateau than for children with no regression or plateau. Children with regression also had elevated autism symptom scores. (study type not specified in abstract)[4].

A study examined levels of social communication behaviours in the onset of autism (study type not specified in abstract):[5]

- At 6 months, children with early onset autism had the lowest social-communication behaviours but with a small decline over the following 18 months, whereas children with regressive autism had significantly higher social-communication but had a rapid decline over time.
- At 24 months all children with autism had significantly lower social-communication behaviour than typically developing children.

A retrospective cohort study[6] investigated the individual and community-level factors that may affect the age of diagnosis of autism:

- Non-white ethnicity and poverty were associated with older age at diagnosis as well as children with higher communication capabilities.
- Higher parental educational status and higher local property values were associated with lower age of diagnosis.

The Evidence Update found studies suggesting that differences in symptoms of autism may exist between girls and boys which could contribute to under-recognition of autism in girls. The guideline already recommends that when considering the possibility of autism practitioners should be aware that autism may be under-diagnosed in girls, it was considered

unlikely that this evidence would impact on current guideline recommendations.

4-year surveillance summary
Five studies were found reporting on signs and symptoms of autism:

Pre-school children (0–5 years)

An observational study[7] found that head lag at 36 months is linked with autism spectrum disorder, particularly in high risk infants.

Primary school age

One study (study type not specified in abstract)[8] found that children with ASD performed worse in a task aimed at testing catching ability compared to age-matched non-verbal and receptive language controls.

Mixed age groups

Three studies were identified in mixed age groups:

- The majority of children with autism experienced motor difficulty or were at risk for motor delay when compared to age-matched typically developing children (study type not specified in abstract)[9].
- Anger was commonly experienced by young people with Asperger's syndrome (AS) (study type not specified in abstract)[10].
- The key clinical features reported were poor communication skills and repetitive and stereotyped patterns of behaviour (study type not specified in abstract)[11].

The 4-year surveillance review found new evidence on signs and symptoms which was broadly consistent with the signs and symptoms of possible autism listed within the guideline. It was considered unlikely that this evidence would impact on current guideline recommendations.

6-year surveillance summary
Three studies were found reporting on signs and symptoms of autism:

- Both facial emotion and affective prosody were impaired in children with ASD and aggravated by the presence of attention deficit hyperactivity disorder (ADHD). An intermediate level of emotion recognition was found in unaffected siblings (study type not specified in abstract)[12].
- Infants with autism used less complex modulated productions compared to infants without autism (study type not specified in abstract)[13].
- Absence of gaze aversion and absence of endpoint nystagmus were associated to autism in preterm infants at the age of 2 years (study type not specified in abstract)[14].

Topic expert feedback
A topic expert referred to an observational study[15] reporting that children with better communication skills and female children with complex phrase speech were diagnosed later (age at diagnosis and study type was not specified in the abstract).

A topic expert suggested to consider a study[16] on factors associated with age at ASD diagnosis (n=2134 children). The study reported that age at diagnosis in the UK has not decreased between 2004 and 2014 and that the median age for all ASD diagnosis was 55 months. Earlier age of autism diagnosis was associated with language regression, language delay, lower socioeconomic status, and greater degree of support required.

Impact statement
This cumulative evidence is generally consistent with current recommendations, which provide guidance to help identify signs and symptoms of possible autism.

New evidence is unlikely to change guideline recommendations.

128 – 01 **b) When should a child or young person be referred for diagnostic assessment?**

Recommendations derived from this question

Recommendations 1.1.8 and 1.3.1 – 1.3.11 (see listed above for question 128-01 a).

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
Three studies were found about the level of parental concern of possible autism:

- More children met the Autism Spectrum Conditions (ASC) criteria whose parents had reported strong parental concern compared to parents who reported minor concern (population-based study)[17].
- No parental concerns were present in children who screened positive for autism (study type not specified in abstract)[18].
- Children with ASD were younger when parents first had concerns and first discussed those concerns with a provider compared to children with intellectual disability/developmental delay (survey)[19].

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
This evidence is generally consistent with current recommendations, which suggest taking into account parental concern when considering referral of children and young people to the autism team.

New evidence is unlikely to change guideline recommendations.

Following referral

Referring children and young people to the autism team

After referral to the autism team

Autism diagnostic assessment for children and young people

128 – 02 **In children with suspected autism (based on signs and symptoms) what information assists in the decision to refer for a formal autism diagnostic assessment?**

Subquestion

a) Are there tools to identify an increased likelihood of autism that are effective in assessing the need for specialist autism assessment?

Recommendations derived from this question

1.3.5 Be aware that tools to identify children and young people with an increased likelihood of autism may be useful in gathering information about signs and symptoms of autism in a structured way but are not essential and should not be used to make or rule out a diagnosis of autism. Also be aware that:

- a positive score on tools to identify an increased likelihood of autism may support a decision to refer but can also be for reasons other than autism
- a negative score does not rule out autism.

Surveillance decision

This review question should not be updated.

2-year evidence update summary

Four studies evaluated accuracy (sensitivity and specificity) of the following tools which identified children with an increased likelihood of autism:

- Manchester Inventory for Playground Observation (MIPO) (study type not specified in abstract)[20]
- Screen for Social Interaction (SSI) (study type not specified in abstract)[21]
- Child Symptom Inventory-4 (CSI-4) (study type not specified in abstract)[22]
- Social Communication Questionnaire (SCQ) (study type not specified in abstract)[23]

During the Evidence Update it was concluded that there was no consistent evidence across the studies which confirmed one tool as meeting the Guideline Committee pre-defined acceptable level for predictive accuracy (sensitivity and specificity of at least 80%). Therefore, it was considered unlikely that the new evidence would impact on current recommendations.

4-year surveillance summary

Twenty-one studies evaluated accuracy (sensitivity and specificity) of the following tools which identified children with an increased likelihood of autism:

- Autism-spectrum quotient (AQ) (observational study)[24]
- Child Behaviour Checklist (CBCL) (observational study)[25]
- Combined use of the Child Behaviour Checklist and the Teacher's Report Form (CBCL/TRF) (observational study)[26]
- Parent's Observations of Social Interactions (POSI) (study type not specified in abstract)[27]
- Strengths and Difficulties Questionnaire (SDQ) (study type not specified in abstract)[28,29]
- Modified Checklist for Autism in Toddlers (M-CHAT) (study type not specified in abstract)[30-34]
- Checklist for Autism in Toddlers-23 (CHAT-23) (study type not specified in abstract)[35]
- PreAut Grid (study type not specified in abstract)[36]
- Three-Item Direct Observation Screen (TIDOS) and Social Communication Questionnaire (SCQ) (study type not specified in abstract)[37]
- Autism-Tics, ADHD, and other Co-morbidities inventory (A-TAC) (study type not specified in abstract)[38]
- Toddler autism screening questionnaire (study type not specified in abstract)[39]
- Social development questionnaire (SIQ) (study type not specified in abstract)[40]
- First Year Inventory (FYI) (study type not specified in abstract)[41,42]
- Social Responsiveness Scale (SRS) (study type not specified in abstract)[43,44]

During the 4-year surveillance review, it was concluded that there was no consistent evidence across the studies which confirmed one tool as meeting the Guideline Committee pre-defined acceptable level for predictive accuracy (sensitivity and specificity of at least 80%). Therefore, it was considered unlikely that

the new evidence would impact on current recommendations.

6-year surveillance summary

Eleven new studies evaluated accuracy (sensitivity and specificity) of the following tools which identified children with an increased likelihood of autism:

- Autism Detection in Early Childhood (ADEC) (screening study, study type not specified in abstract for reference 45)[45,46]
- Checklist for Autism Spectrum Disorder (CASD) (study type not specified in abstract)[47]
- Childhood Autism Spectrum Test (CAST) (study type not specified in abstract)[48]
- Child Behaviour Checklist for children aged 18 months to 5 years (CBCL) (study type not specified in abstract for both references)[49,50]
- Modified Checklist for Autism in Toddlers (M-CHAT) (reference 51 is a population-based longitudinal study, study type was not specified in abstract for references 50 and 52)[51-53]
- Rapid Interactive Screening Test for Autism in Toddlers (RITA-T) (study type not specified in abstract)[54]
- Social Responsiveness Scale (SRS) (study type not specified in abstract)[55]

Three of these tools (CASD, M-CHAT, and RITA-T) partially met the threshold for accuracy (sensitivity and specificity) which was agreed by the Guideline Committee (sensitivity and specificity 80% with a lower 95% confidence interval threshold of 70%). However, none of these studies reported confidence intervals in the abstract.

Topic expert feedback

A topic expert referred to a study[56] evaluating the accuracy of the Development and Well-Being Assessment (DAWBA) in children and adolescents. Although sensitivity and specificity were over 80%, the confidence intervals were not reported in the abstract (study type not specified in abstract).

Following the prioritisation phase, a topic expert suggested to consider a systematic review[57] on approaches to enhance early detection of ASD. The systematic review categorised these approaches into awareness, routine screening and practice improvement to enhance screening. It was concluded that time to diagnosis was largely untested.

Impact statement

Through surveillance, a range of studies were identified focusing on different tools. This cumulative evidence was insufficient to show clear differences between the tools. Therefore, it was concluded that this evidence is unlikely to impact on current recommendations.

New evidence is unlikely to change guideline recommendations.

Subquestion

b) What information about the child and family increases the likelihood of a diagnosis of autism and would assist in the decision to refer for a formal autism diagnostic assessment?

- risk factors (part 1).

Recommendations derived from this question

1.3.3 Consider referring children and young people to the autism team if you are concerned about possible autism on the basis of reported or observed signs and/or symptoms (see tables 1–3 in appendix C). Take account of:

- the severity and duration of the signs and/or symptoms
- the extent to which the signs and/or symptoms are present across different settings (for example, home and school)
- the impact of the signs and/or symptoms on the child or young person and on their family
- the level of parental or carer concern and, if appropriate, the concerns of the child or young person

- factors associated with an increased prevalence of autism (see box 1)
- the likelihood of an alternative diagnosis.

Box 1 Factors associated with an increased prevalence of autism

- A sibling with autism
- Birth defects associated with central nervous system malformation and/or dysfunction, including cerebral palsy
- Gestational age less than 35 weeks
- Parental schizophrenia-like psychosis or affective disorder
- Maternal use of sodium valproate in pregnancy
- Intellectual disability
- Neonatal encephalopathy or epileptic encephalopathy, including infantile spasms
- Chromosomal disorders such as Down's syndrome
- Genetic disorders such as fragile X
- Muscular dystrophy
- Neurofibromatosis
- Tuberous sclerosis

1.3.7 When referring children and young people to the autism team, include in the referral letter the following information, if available:

- antenatal and perinatal history
- developmental milestones
- factors associated with an increased prevalence of autism (see box 1)
- relevant medical history and investigations
- information from previous assessments.

1.4.4 When deciding whether to carry out an autism diagnostic assessment, take account of the following (unless the child is under 3 years and has regression in language or social skills – see recommendation 1.4.2):

- the severity and duration of the signs and/or symptoms
- the extent to which the signs and/or symptoms are present across different settings (for example, home and school)
- the impact of the signs and/or symptoms on the child or young person and on their family or carer
- the level of parental or carer concern, and if appropriate the concerns of the child or young person
- factors associated with an increased prevalence of autism (see box 1)
- the likelihood of an alternative diagnosis.

Surveillance decision

This review question should not be updated.

2-year evidence update summary

Familiar or parental factors

A retrospective secondary analysis of a longitudinal UK cohort study was found providing new evidence on risk factors for autism:[58]

- Male gender

- Older maternal age than overall population
- Children who were born first compared to subsequent children

During the Evidence Update, it was concluded that additional consistent evidence would be needed before considering these new risk factors for inclusion in the guideline.

4-year surveillance summary

Thirty-nine studies were found providing new evidence on risk factors for autism:

All factors

- Male gender, low birth weight, low level of education of the mother, social, behavioural, language, psychomotor and eating problems (study type not specified in abstract)[59]

Familiar or parental factors

- Finnish second-generation migrants (case-control study)[60]
- Maternal diabetes (systematic review and meta-analysis of observational studies)[61]
- Advancing paternal age (population-based case-control study, case-control study, population-based cohort study)[62-64], particularly for mothers aged 40-45 and fathers aged 55-59 (population-based cohort study)[64]
- Maternal exposure to childhood abuse (longitudinal cohort study)[65]
- Family history of schizophrenia (parent or sibling) (case-control study)[66]
- Decreased risk of ASD with increasing parity and increased risk of autism for the second born child compared to the first (study type not specified in abstract)[67]
- Maternal and paternal full-siblings compared to half-siblings (cohort study)[68]

Perinatal or neonatal factors

- Low birth weight, gestational age less than 32 weeks and small for gestational age (case-control study)[69]
- Pre-term birth (population-based quasi-experimental study, population-based study, retrospective cohort study, study type not specified in abstract for references 68 and 72)[70-74]
- Foetal growth both below and above the mean for gestational age (case-control study)[75]
- Type of white matter injury and ventricular enlargement (study type not specified in abstract)[76]

Pregnancy-related factors

- Mothers taking medications and smoking during pregnancy (case-control study)[77]
- For inter pregnancy intervals shorter than 12 months, increased risk of autistic disorder in the second-born child (study type not specified in abstract)[78]
- Maternal high blood pressure, low Apgar scores (<7) and neonatal treatment with monitoring (study type not specified in abstract)[79]
- Maternal smoking in pregnancy was not link to ASD in a case-control study[80] but another case-control study[81] found a small increase in risk of pervasive developmental disorder
- Low maternal intake of polyunsaturated fat before or during pregnancy (study type not specified in abstract)[82]

Lack of maternal use of prenatal folic acid supplements (prospective cohort study)[83]

- No association between maternal autoimmune disease and ASD alone (study type not specified in abstract)[84]
- Women with infections diagnosed during a hospital admission and multiple infections during pregnancy (case-control study)[85]
- Maternal fever during pregnancy but this risk was diminished in mothers who reported taking antipyretic medications (study type not specified in abstract)[86]
- Pregnancy weight gain (study type not specified in abstract)[87]
- Maternal use of valproate during pregnancy (study type not specified in abstract)[88]
- Maternal use of antidepressants during pregnancy (case-control study)[89]
- Two studies found no significant link between prenatal exposure to antidepressants and ASD (study type not specified in abstract for reference 88, reference 89 was a cohort study)[90,91]
- Maternal hormonal interventions (study type not specified in abstract)[92]
- No increase in risk of ASD in children born after in vitro fertilisation (IVF) (case-control study)[93]

- Children born after ovulation induction with or without insemination (prospective cohort study)[94]
- IVF treatment using intracytoplasmic sperm injection for male infertility (prospective cohort study)[95]
- Severe maternal hypothyroxinaemia at 6-18 weeks gestational age (study type not specified in abstract)[96]

Environmental factors

- Long-term exposure to air pollution (increasing ozone, carbon monoxide, nitrogen dioxide, and sulphur dioxide levels) (cohort study)[97]

During the 4-year surveillance review, it was concluded that additional consistent evidence would be needed before considering these new risk factors for inclusion in the guideline.

6-year surveillance summary

Twenty-one studies provided new evidence on risk factors for autism:

- Early life exposure of household pesticides (case-control study)[98]
- Maternal obesity in preterm children (prospective cohort study)[99]
- Maternal overweight (population-based cohort study)[100] and obesity[100,101] (meta-analysis of observational studies)
- Paternal obesity (population-based cohort studies)[100,102]
- Systemic lupus erythematosus (SLE) during pregnancy (population study)[103]
- Maternal smoking during pregnancy (two meta-analysis, each one included 15 observational studies)[104,105]
- Maternal chemical intolerance (case-control study)[106]
- Rarely/never taking prenatal vitamins (prospective cohort study)[107]
- Antidepressants prior to pregnancy (study type not specified in abstract)[108]
- Prenatal exposure to maternal depressive symptoms without selective serotonin reuptake inhibitors (SSRIs) (population-based study)[109]
- Prenatal and during pregnancy exposure to SSRIs (systematic review of observational studies and meta-analysis of case-control studies)[110]
- Assisted reproductive technology with intracytoplasmic sperm injection (ICSI) (population-based retrospective cohort study)[111]
- Thyroid stimulating hormone levels during pregnancy (study type not specified in abstract)[112]
- Older paternal and maternal age (study type not specified in abstract)[113]
- Paternal elevated scores in the Social Responsiveness Scale (SRS) (nested case-control study)[114]
- Organic mercury exposure from Thimerosal-containing vaccines (case control study)[115]
- Late and moderately preterm (32-36 weeks) infants (population-based prospective cohort study)[116]
- Maternal autoimmune diseases (systematic review and meta-analysis of observational studies)[117]
- Preeclampsia (population-based case-control study)[118]
- Parental impaired recognition of ambiguous expressions (study type not specified in abstract)[119]

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Through surveillance, a vast amount of evidence was identified evaluating different risk factors. All of these factors but not maternal smoking during pregnancy[104,105] and parental impaired recognition of ambiguous expressions reported an odds ratio (OR) >1.25 which was considered as a clinically important risk factor by the Guideline Committee during the development of this guideline. However, during guideline development, the Guideline Committee members also considered the quality of evidence and practical use for the inclusion of risk factors in the recommendations (1.3.3, 1.3.7, 1.4.4). In this surveillance review, a critical evaluation of the studies was not done in detail because surveillance review looks at abstracts only. Therefore, the clinical expertise of the Guideline Committee members is necessary to make a conclusion on whether to add these new risk factors into the list related to recommendations 1.3.3, 1.3.7, 1.4.4.

New evidence identified that may change current recommendations.

Subquestion

b) What information about the child and family increases the likelihood of a diagnosis of autism and would assist in the decision to refer for a formal autism diagnostic assessment?

- conditions with an increased risk of autism (part 2).

Recommendations derived from this question

1.3.3 Consider referring children and young people to the autism team if you are concerned about possible autism on the basis of reported or observed signs and/or symptoms (see tables 1–3 in appendix C). Take account of:

- the severity and duration of the signs and/or symptoms
- the extent to which the signs and/or symptoms are present across different settings (for example, home and school)
- the impact of the signs and/or symptoms on the child or young person and on their family
- the level of parental or carer concern and, if appropriate, the concerns of the child or young person
- factors associated with an increased prevalence of autism (see box 1)
- the likelihood of an alternative diagnosis.

Box 1 Factors associated with an increased prevalence of autism

- A sibling with autism
- Birth defects associated with central nervous system malformation and/or dysfunction, including cerebral palsy
- Gestational age less than 35 weeks
- Parental schizophrenia-like psychosis or affective disorder
- Maternal use of sodium valproate in pregnancy
- Intellectual disability
- Neonatal encephalopathy or epileptic encephalopathy, including infantile spasms
- Chromosomal disorders such as Down's syndrome
- Genetic disorders such as fragile X
- Muscular dystrophy
- Neurofibromatosis
- Tuberous sclerosis

1.3.7 When referring children and young people to the autism team, include in the referral letter the following information, if available:

- antenatal and perinatal history
- developmental milestones
- factors associated with an increased prevalence of autism (see box 1)
- relevant medical history and investigations
- information from previous assessments.

1.4.4 When deciding whether to carry out an autism diagnostic assessment, take account of the following (unless the child is under 3 years and has regression in language or social skills – see recommendation 1.4.2):

- the severity and duration of the signs and/or symptoms
- the extent to which the signs and/or symptoms are present across different settings (for example, home and school)
- the impact of the signs and/or symptoms on the child or young person and on their family or carer
- the level of parental or carer concern, and if appropriate the concerns of the child or young person
- factors associated with an increased prevalence of autism (see box 1)
- the likelihood of an alternative diagnosis.

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
An observational study[120] reported that 57% of cases from a Neurofibromatosis Type 1 (NF1) registry were categorised as ASD or broad-ASD, which translated into a population prevalence estimate of 45.7% with some form of ASD.

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
At the 4-year surveillance review, it was considered that this evidence was unlikely to change the current guideline recommendation which states that information on associated factors, including Neurofibromatosis, should be included in the referral letter to the autism team.

New evidence is unlikely to change guideline recommendations.

Subquestion

c) What information from other sources is useful as contextual information: for example information about how the child functions in different environments such as school and home, social care reports (e.g. for looked after children) and information from other agencies?

Recommendations derived from this question

1.4.1 When a child or young person is referred to the autism team, at least one member of the autism team should consider whether to carry out:

- an autism diagnostic assessment and/or
- an alternative assessment.

1.4.2 Carry out an autism diagnostic assessment if there is regression in language or social skills in a child younger than 3 years.

1.4.3 Refer first to a paediatrician or paediatric neurologist (if this has not already happened) children or young people:

- older than 3 years with regression in language

- of any age with regression in motor skills.

The paediatrician or paediatric neurologist can refer back to the autism team if necessary.

1.4.4 When deciding whether to carry out an autism diagnostic assessment, take account of the following (unless the child is under 3 years and has regression in language or social skills – see recommendation 1.4.2):

- the severity and duration of the signs and/or symptoms
- the extent to which the signs and/or symptoms are present across different settings (for example, home and school)
- the impact of the signs and/or symptoms on the child or young person and on their family or carer
- the level of parental or carer concern, and if appropriate the concerns of the child or young person
- factors associated with an increased prevalence of autism (see box 1)
- the likelihood of an alternative diagnosis.

1.4.5 If there is insufficient information to decide whether an autism diagnostic assessment is needed, gather any available information from healthcare professionals. With consent from parents or carers and, if appropriate, the child or young person, seek information from schools or other agencies.

1.4.6 If there is uncertainty about whether an autism diagnostic assessment is needed after information has been gathered, offer a consultation to gather information directly from the child or young person and their family or carers.

1.4.7 Once it has been decided to carry out an autism diagnostic assessment, with consent from parents or carers (and the child or young person if appropriate):

- seek a report from the pre-school or school if one has not already been made available
- gather any additional health or social care information, including results from hearing and vision assessments.

1.4.8 Avoid repeated information gathering and assessments by efficient communication between professionals and agencies.

1.5.1 Start the autism diagnostic assessment within 3 months of the referral to the autism team.

Surveillance decision

This review question should not be updated.

2-year evidence update summary
A prospective cohort study[121] was identified which suggested that children who have been arrested for a first offence may have higher levels of symptoms of autism than the general population, but lower levels of symptoms than those who have had a clinical diagnosis of autism. However, there was a lack of clinical diagnosis of autism in the sample.

4-year surveillance summary
No relevant evidence was identified

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
The 2-year evidence update concluded that the new evidence was unlikely to impact on current guideline recommendations which states that information from other agencies should be sought if there is insufficient information to decide whether an autism diagnostic assessment is needed, and that important information about early development may not be readily available for some children and young people in the criminal justice system. No new evidence was identified through the 4-year

or 6-year surveillance to change this conclusion.	New evidence is unlikely to change guideline recommendations.

Diagnostic assessment

Local pathway for recognition, referral and diagnostic assessment of possible autism

Autism diagnostic assessment for children and young people

After the autism diagnostic assessment

Communicating the results from the autism diagnostic assessment

128 – 03 What should be the components of the diagnostic assessment? When should they be undertaken, in what subgroups and in what order?

Subquestion

a) assessment tools specific to autism: for example Autism Diagnostic Interview and Autism Diagnostic Interview – Revised (ADI/ADI-R), Developmental, Dimensional and Diagnostic Interview (3di), Diagnostic Interview for Social and Communication Disorders (DISCO), Autism Diagnostic Observation Schedule (ADOS), Gilliam Autism Rating Scale (GARS).

Recommendations derived from this question

1.1.3 In each area a multidisciplinary group (the autism team) should be set up. The core membership should include a:

- paediatrician and/or child and adolescent psychiatrist
- speech and language therapist
- clinical and/or educational psychologist.

1.1.4 The autism team should either include or have regular access to the following professionals if they are not already in the team:

- paediatrician or paediatric neurologist
- child and adolescent psychiatrist
- educational psychologist
- clinical psychologist
- occupational therapist.

1.1.5 Consider including in the autism team (or arranging access for the team to) other relevant professionals who may be able to contribute to the autism diagnostic assessment. For example, a specialist health visitor or nurse, specialist teacher or social worker.

1.1.6 The autism team should have the skills and competencies to:

- carry out an autism diagnostic assessment
- communicate with children and young people with suspected or known autism, and with their parents and carers, and sensitively share the diagnosis with them.

1.1.7 Autism team members should:

- provide advice to professionals about whether to refer children and young people for autism diagnostic assessments

- decide on the assessment needs of those referred or when referral to another service will be needed
- carry out the autism diagnostic assessment
- share the outcome of the autism diagnostic assessment with parents and carers, and with children and young people if appropriate
- with parent or carer consent and, if appropriate, the consent of the child or young person, share information from the autism diagnostic assessment directly with relevant services, for example through a school visit by an autism team member
- offer information to children, young people and parents and carers about appropriate services and support.

1.1.9 The autism team should either have the skills (or have access to professionals that have the skills) needed to carry out an autism diagnostic assessment, for children and young people with special circumstances including:

- coexisting conditions such as severe visual and hearing impairments, motor disorders including cerebral palsy, severe intellectual disability, complex language disorders or complex mental health disorders
- looked-after children and young people.

1.1.10 If young people present at the time of transition to adult services, the autism team should consider carrying out the autism diagnostic assessment jointly with the adult autism team, regardless of the young person's intellectual ability.

1.5.5 Include in every autism diagnostic assessment:

- detailed questions about parent's or carer's concerns and, if appropriate, the child's or young person's concerns
- details of the child's or young person's experiences of home life, education and social care
- a developmental history, focusing on developmental and behavioural features consistent with ICD-10 or DSM-IV criteria (consider using an autism-specific tool to gather this information)
- assessment (through interaction with and observation of the child or young person) of social and communication skills and behaviours, focusing on features consistent with ICD-10 or DSM-IV criteria (consider using an autism-specific tool to gather this information)
- a medical history, including prenatal, perinatal and family history, and past and current health conditions
- a physical examination
- consideration of the differential diagnosis (see recommendation 1.5.7)
- systematic assessment for conditions that may coexist with autism (see recommendation 1.5.15)
- development of a profile of the child's or young person's strengths, skills, impairments and needs that can be used to create a needs-based management plan, taking into account family and educational context.
- communication of assessment findings to the parent or carer and, if appropriate, the child or young person.

1.5.6 Perform a general physical examination and look specifically for:

- skin stigmata of neurofibromatosis or tuberous sclerosis using a Wood's light
- signs of injury, for example self-harm* or child maltreatment**
- congenital anomalies and dysmorphic features including macrocephaly or microcephaly.

1.5.8 Consider which assessments are needed to construct a profile for each child or young person, for example:

- intellectual ability and learning style
- academic skills
- speech, language and communication
- fine and gross motor skills
- adaptive behaviour (including self-help skills)
- mental and emotional health (including self-esteem)
- physical health and nutrition
- sensory sensitivities
- behaviour likely to affect day-to-day functioning and social participation
- socialisation skills.

1.5.10 Use information from all sources, together with clinical judgment, to diagnose autism based on ICD-10 or DSM-IV criteria.

1.5.11 Do not rely on any autism-specific diagnostic tool alone to diagnose autism.

1.5.12 Be aware that in some children and young people there may be uncertainty about the diagnosis of autism, particularly in:

- children younger than 24 months
- children or young people with a developmental age of less than 18 months
- children or young people for whom there is a lack of available information about their early life (for example some looked-after or adopted children)
- older teenagers
- children or young people with a complex coexisting mental health disorder (for example ADHD, conduct disorder, a possible attachment disorder), sensory impairment (for example severe hearing or visual impairment), or a motor disorder such as cerebral palsy.

1.5.13 Be aware that some children and young people will have features of behaviour that are seen in the autism spectrum but do not reach the ICD-10 or DSM-IV diagnostic criteria for definitive diagnosis. Based on their profile, consider referring to appropriate services.

1.5.14 If the outcome of the autism diagnostic assessment clearly indicates that the child or young person does not have autism, consider referring them to appropriate services based on their profile.

1.5.16 Be aware that in children and young people with communication difficulties it may be difficult to recognise functional problems or mental health problems.

1.6.3 During the autism diagnostic assessment, consider any potential risk of harm to, and from, the child or young person and take appropriate action.

* See 'Self-harm: the short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care' (NICE clinical guideline 16).

** See 'When to suspect child maltreatment' (NICE clinical guideline 89).

Surveillance decision

This review question should not be updated.

2-year evidence update summary

Seven studies were found evaluating the following assessment tools specific for autism:

- Autism Spectrum Quotient (AQ) and Quantitative Checklist for Autism in Toddlers (Q-CHAT) (study type not specified in abstract)[122]
- Autism Diagnostic Interview-Revised (ADI-R) (cohort studies)[123,124]
- Autism Diagnostic Observation Schedule (ADOS) (cohort study)[125]

- Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) (study type not specified in abstract for reference 124, reference 125 was an observational study)[126,127]
- Social Responsiveness Scale (SRS), ADI-R and ADOS (study type not specified in abstract)[128]

During the Evidence Update, it was concluded that the evidence was consistent with the guideline recommendations which states do not rely on any autism-specific diagnostic tool alone to diagnose autism. As such, the new evidence was unlikely to impact on current guideline recommendations.

4-year surveillance summary
Nine studies were found evaluating the following assessment tools specific for autism:

- Autism Spectrum Disorder Observation for Children (ASD-OC) (study type not specified in abstract)[129]
- Autism Diagnostic Interview-Revised (ADI-R) (study type not specified in abstract)[130,131]
- Autism Diagnostic Observation Schedule-Generic (ADOS) (study type not specified in abstract)[132]
- Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule-Generic (ADOS) (study type not specified in abstract)[133]
- Coolidge Autistic Symptoms Survey (CASS) (study type not specified in abstract)[134]
- Developmental, Dimensional and Diagnostic Interview (3Di) (study type not specified in abstract)[135]
- Childhood Autism Rating Scale Second Edition (CARS2) (study type not specified in abstract)[136]

Childhood Autism Rating Scale-Second Edition-Standard Version (CARS2-ST) (study type not specified in abstract)[137]

During the 4-year surveillance review, it was concluded that the evidence was consistent with the guideline recommendations which states do not rely on any autism-specific diagnostic tool alone to diagnose autism. As such, the new evidence was unlikely to impact on current guideline recommendations.

6-year surveillance summary
Five new studies evaluated accuracy (sensitivity and specificity) of the following assessment tools specific for autism:

- Developmental, Dimensional and Diagnostic Interview (3di) (study type not specified in abstract)[138]
- Autism Diagnostic Interview-Revised (ADI-R) (study type not specified in abstract)[139]
- Autism Diagnostic Observation Schedule (ADOS) (reference 138 is a meta-analysis of cross-sectional studies, study type not specified in abstract for reference 139)[140,141]
- Childhood Autism Rating Scale (CARS) (study type not specified in abstract)[142]

Most of these studies did not meet the threshold for accuracy which was agreed by the Guideline Committee (sensitivity and specificity 80% with a lower 95% confidence interval threshold of 70%). One study reported sensitivity and specificity >80% for autism using the ADOS[141] without reporting confidence intervals in the abstract.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
Through surveillance, a number of assessment tools specific to autism were identified. However, only some of the tools met the Guideline Committee pre-defined acceptable level for predictive accuracy (sensitivity and specificity of at least 80%). There was also no consistent evidence to recommend the use of one specific tool. This cumulative evidence was consistent with the guideline recommendations which states do not rely on any autism-specific diagnostic tool alone to diagnose autism. Therefore, the new evidence was unlikely to impact on current guideline recommendations.

New evidence is unlikely to change guideline recommendations.

Subquestion

b) other assessment tools that help the interpretation of the specific autism tools and ratings scales (for example ADI, 3di, DISCO, ADOS, Gilliam Autism Rating Scale): such as an assessment of intellectual ability or an assessment of receptive and expressive language.

Recommendations derived from this question

Recommendations 1.1.3-1.1.7, 1.1.9-1.1.10, 1.5.5-1.5.6, 1.5.8, 1.5.10-1.5.14, 1.5.16, and 1.6.3 (see listed above for question 128-03 a).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Medical investigations

Biomedical investigations for diagnosis of autism, for example electroencephalography (EEG), brain scan, genetic tests, counselling; investigations for associated medical conditions.

Recommendations derived from this question

1.7.1 Do not routinely perform any medical investigations as part of an autism diagnostic assessment, but consider the following in individual circumstances and based on physical examination, clinical judgment and the child or young person's profile:

- genetic tests, as recommended by your regional genetics centre, if there are specific dysmorphic features, congenital anomalies and/or evidence of intellectual disability
- electroencephalography if there is suspicion of epilepsy*.

* See 'The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care' (NICE clinical guideline 20).

Surveillance decision

This review question should not be updated.

2-year evidence update summary

Two studies were found reporting the use of the following medical investigations:

- A study of electroencephalography (EEG) coherence reported that 40 coherence factors were found to account for 51% of variation between the autism and control groups (study type not specified in abstract)[143].
- A cohort study[144] reported that the diagnostic yield of the genetic testing was low with just 6% of cases found to have a genetic disorder.

During the Evidence Update, it was concluded that the evidence was consistent with the recommendation in the guideline which states do not routinely perform any medical investigations as part of an autism diagnostic assessment but consider genetic tests and electroencephalography dependent on individual circumstances.

4-year surveillance summary

Thirty-one studies were found reporting the use of the following medical investigations:

- A study examined scalp hair concentrations of trace elements in autistic children and reported that 29.7% were deficient in zinc and 17.6% in magnesium and 17.2% suffered from high burdens of aluminium (study type not specified in abstract)[145].

Neuroimaging

- The results of a systematic review and meta-analysis[146] suggested that there were significant differences in the superior longitudinal fasciculus, uncinate fasciculus, and corpus callosum in people with ASD compared to typically developing individuals.
- A study using magnetic resonance spectroscopy suggested hyperglutamatergia and other neurometabolic abnormalities in the pregenual anterior cingulate cortex (pACC) in children with ASD compared to controls. (study type not specified in abstract)[147].
- A study using transcranial ultrasonography (TUS) via the temporal bone found that children with autism had higher scores for both extra-axial spaces and cortical dysplasia than their neurotypical siblings, suggesting TUS as a potential screening technique for children at risk of ASDs (study type not specified in abstract)[148].
- A study using positron emission tomography (PET) found that 87% of children with autism had decreased metabolic activity in the temporal lobe, 60% had decreased activity in the frontal lobe and 47% had decreased activity in the parietal lobe (study type not specified in abstract)[149].
- A study using magnetic resonance spectroscopy and spectral editing methods found that there were reduced levels of Creatine-normalised Gamma-Aminobutyric acid (GABA) + ratios in the motor and auditory regions of interest in children with ASD compared to controls. Mean deficiencies were approximately 11% from the motor region interest and 22% in the auditory region. (study type not specified in abstract)[150].
- A case-control study[151] showed that maps of salience network hyperconnectivity discriminated children with ASD from typically developing (TD).

Blood and urine tests

- Mean serum level of the desert hedgehog (Dhh) protein was lower in patients with autism than the level of normal controls but that there was no link between serum level and age, gender or autistic severity (study type not specified in abstract)[152].
- Children with autism had higher serum levels of macrophage-derived chemokine (MDC) and thymus and activation-regulated chemokine (TARC). Increased levels were particularly associated with severe autism compared to mild to moderate autism (study type not specified in abstract)[153].
- Children with autism had higher serum levels of IL-17A (a pro-inflammatory cytokine). Increased serum levels were found in 48.9% of the autism group. Levels of IL-17A were correlated with severity of autism (study type not specified in abstract)[154].
- Humoral immunity profile had a sensitivity of 79% and a specificity of 83% for identifying children with autism (study type not specified in abstract)[155].
- A study measured the mRNA expression profile in peripheral blood mononuclear cells. Potential biomarkers were identified in half the group which were reported to have high diagnostic accuracy in the remaining half, however, no figures were presented in the abstract (study type not specified in abstract)[156].
- Children with ASD had lower mean serum 25-hydroxyvitamin D (25(OH) D) levels compared to controls and that there is a link between serum and autism severity (study type not specified in abstract)[157].
- A study investigating the antioxidant specificities in plasma and red blood cell haemolysate found that there were differences in some of the antioxidant enzyme levels in children with autism (study type not specified in abstract)[158].
- Children with autism had higher corticosteroid excretion levels compared to controls and those with low and medium autism severity had high level of corticosteroids in the urine (study type not specified in abstract)[159].
- Boys with autism had higher concentrations of pentacarboxyl and coproporphyrins compared to controls. Sensitivity of both pentacarboxyl and coproporphyrins for ASD were low at 30% and 33% respectively, however specificities were high at 94% for both (study type not specified in abstract)[160].
- A study found that 87% of individuals with ASDs had increased levels of urine aspartic

acid, 69% had increased levels of plasma taurine, and 72% had reduced plasma cysteine (study type not specified in abstract)[161].

Genetic tests

- A study reported that fragile X site and FMR1 full mutation allele were identified in 4.6% and 6.15% of children with ASD respectively (study type not specified in abstract)[162].
- A study used a custom-designed oligonucleotide array comparative genomic hybridisation and identified 16 copy-number variants (CNVs) in a cohort of participants with ASDs of which 5.5% were considered likely to contribute to ASDs[163].
- A study used both single-nucleotide polymorphism (SNP) and comparative genomic hybridisation (CGH) arrays. 64% of CNVs that were identified were found exclusively by the CGH array, including several that impact on previously reported ASD genes as well as novel ASD candidate genes (study type not specified in abstract)[164].
- A study in children with mental retardation and autism reported that using high-resolution comparative genomic methods for hybridisation (HRCGH), genomic rearrangements were identified in 46% of cases. Molecular karyotyping (array CGH) identified different genomic abnormalities and genomic variations in 88% of cases and unbalanced genomic rearrangements in 52% of cases (study type not specified in abstract)[165].
- A study used chromosomal microarray analysis to identify copy number variants (CNVs) in patients with autism or autism spectrum disorders (ASD) or developmental delay/learning disability. It was found that 21% of participants had abnormal microarray results (study type not specified in abstract)[166].
- A study used chromosomal microarray (CMA) as a clinical diagnostic test finding that 91 CNVs were detected in 22% of participants of which 23% had intellectual disability and ASDs (study type not specified in abstract)[167].
- A case-control study[168] analysed the frequency of the methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism using a polymerase chain reaction-restriction fragment length polymorphism assay. The results indicated that 16.1% of children with autism had the genotype MTHFR 677TT compared to 8.6% of controls.
- A case control study[169] used polymerase chain reaction-restriction fragment length polymorphism to assess the impact of the catechol-O-methyltransferase (COMT) gene Val158Met polymorphism and found that the frequency of the Val158 genotype in children with ASD was lower than in healthy controls.
- A study(study type not specified in abstract)[170] used comparative gene expression profiling analysis to identify 252 differentially expressed probe sets representing 202 genes between a group of participants with ASD and controls. Further analysis of one of the differentially expressed genes, using real-time quantitative PCR, indicated elevation of the FOXP1 gene transcript of LCL in ASD participants.
- Using Affymetrix SNP microarrays, a case control study[171] identified a number of genetic variants within the metabotropic glutamate receptor 7 (GRM7) gene associated with ASD.
- A study (study type not specified in abstract)[172] was identified which used whole-genome sequencing (WGS) to detect de novo or rare inherited genetic variants likely to be associated with ASD. Deleterious de novo mutations were found in 19% of families and X-linked or autosomal inherited alterations in 31% of families.
- A study (study type not specified in abstract)[173] reported an association between two genetic markers (rs4307059 T allele and rs35678 TC genotype) and ASDs.
- The AFF2 genomic region was sequenced in males with ASD. The results indicated that compared to controls, there was a significant enrichment in participants with ASD (study type not specified in abstract)[174].
- The results of a meta-analysis[175] showed that there was an increased risk of ASD associated with the

methylenetetrahydrofolate reductase C677T polymorphism, although further analysis found that the increased ASD risk from the C677T polymorphism only occurred in children in countries without food fortification.

- A study (study type not specified in abstract)[176] identified several recurrent large hotspots of copy-number variation which are more likely to be identified in individuals with autism than in those with developmental delay.

During the 4-year surveillance review, it was concluded that the evidence was consistent with the recommendation in the guideline which states do not routinely perform any medical investigations as part of an autism diagnostic assessment but consider genetic tests and electroencephalography dependent on individual circumstances.

6-year surveillance summary

Five new studies reported the use of the following blood tests:

- Serum brain-derived neurotrophic factor (BDNF) was an independent indicator of ASD (study type not specified in abstract for reference 175 and pilot study for reference 176)[177,178].
- Serum thioredoxin (TRX) was an independent diagnosis marker of ASD (study type not specified in abstract)[179].
- Plasma levels of lipoxin A4 (LXA4) were significantly lower in autistic children compared with the normal children (study type not specified in abstract)[180].
- Plasma neopterin levels was an independent diagnosis indicator of ASD (study type not specified in abstract)[181].

Two new studies reported the use of magnetic resonance imaging (MRI) scans:

- Minor brain abnormalities were more frequent in children with autism compared to controls (prevalence study)[182].
- A high rate of brain abnormalities was found in children with autistic spectrum disorders (study type not specified in abstract)[183].

Two new studies reported the use of electroencephalography (EEG):

- Both studies reported brain abnormalities in children and young people with ASD (reference 182 is a retrospective study, study type not specified in abstract for reference 183)[184,185].

There were 9 new studies reporting genes related to ASD:

- Loci on chromosome 20p13, 6q27, 8q13.2, 1p31.3 (for males), and 8p21.2 (for females) were associated with ASD (study type not specified in abstract)[186].
- SLC25A12 variants (rs2056202 and rs2292813) were associated with decreased risk of ASD (meta-analysis of case-control and transmission disequilibrium test studies)[187].
- Monoamine oxidase A (MAOA) promoter polymorphism was associated with idiopathic autism and fragile X syndrome (FXS) (study type not specified in abstract)[188].
- Two polymorphisms in the HTR2B gene (rs10194776 and rs16827801) were associated with ASD phenotypes (cohort study)[189].
- A single nucleotide polymorphism (SNP) (rs2158836) was associated with more severe symptoms of ASD (study type not specified in abstract)[190].
- Five SNPs (rs2317385, rs5918, rs15908, rs12603582, rs3809865) were associated with ASD (study type not specified in abstract)[191].
- Mitogen inducible gene 6 (MIG-6) levels in children with autism were significantly lower than neurotypical controls (study type not specified in abstract)[192].
- 39 DNA sequence variants identified 36 ASD risk genes (study type not specified in abstract)[193].
- Most children with SHANK3 deficiency met criteria for ASD (prospective study)[194].

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Through surveillance, 51 studies were identified on medical examinations. However, there was a substantial variability of the type of genetic investigations, neuroimaging techniques, and blood and urinary laboratory tests. Most of the studies reported on abnormalities related to ASD rather than on coexisting conditions. The evidence was not

consistent to suggest specific medical investigations to diagnose ASD. It was concluded that this cumulative evidence was consistent with the recommendation in the guideline which states do not routinely perform any medical investigations as part of an autism diagnostic assessment but consider genetic tests and electroencephalography dependent on individual circumstances.

New evidence is unlikely to change guideline recommendations.

Differential diagnosis

Autism diagnostic assessment for children and young people

128 – 04 a) What are the most important differential diagnoses of autism?

Recommendations derived from this question

1.5.7 Consider the following differential diagnoses for autism and whether specific assessments are needed to help interpret the autism history and observations:

- Neurodevelopmental disorders:
  - specific language delay or disorder
  - intellectual disability or global developmental delay
  - developmental coordination disorder (DCD).
- Mental and behavioural disorders:
  - attention deficit hyperactivity disorder (ADHD)
  - mood disorder
  - anxiety disorder
  - oppositional defiant disorder (ODD)
  - conduct disorder
  - obsessive compulsive disorder (OCD)
  - psychosis.
- Conditions in which there is developmental regression:
  - Rett syndrome
  - epileptic encephalopathy.
- Other conditions:
  - severe hearing impairment
  - severe visual impairment
  - maltreatment
  - selective mutism.

Surveillance decision

This review question should not be updated.

2-year evidence update summary No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified

6-year surveillance summary
Four studies were found about differential diagnoses for autism:

- Attachment disorder was found in 42% and Pervasive Developmental Disorder (PDD) in 27% of children with intellectual disability. (study type not specified in abstract)[195].
- Clinical diagnosis of attention deficit hyperactivity disorder (ADHD) was found in 68.1% of participants with ASD (study type not specified in abstract)[196].
- Children with ADHD had more ASD symptoms than non-ADHD controls (community-based study)[197].
- 20% of children with ASD were initially diagnosed with ADHD. These children were diagnosed with ASD 3 years after children in whom ADHD was diagnosed at the same time or after ASD (national survey)[198].

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
New evidence was found about attachment disorder and ADHD as differential diagnoses for ASD which are already considered by recommendation 1.5.7. Therefore, new evidence is consistent with current recommendation.

New evidence is unlikely to change guideline recommendations.

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128 – 04 b) What features observed during diagnosis reliably differentiate other conditions from autism?

Recommendations derived from this question

1.5.7 Consider the following differential diagnoses for autism and whether specific assessments are needed to help interpret the autism history and observations:

- Neurodevelopmental disorders:
  - specific language delay or disorder
  - intellectual disability or global developmental delay
  - developmental coordination disorder (DCD).
- Mental and behavioural disorders:
  - attention deficit hyperactivity disorder (ADHD)
  - mood disorder
  - anxiety disorder
  - oppositional defiant disorder (ODD)
  - conduct disorder
  - obsessive compulsive disorder (OCD)
  - psychosis.
- Conditions in which there is developmental regression:
  - Rett syndrome
  - epileptic encephalopathy.
- Other conditions:
  - severe hearing impairment
  - severe visual impairment

- maltreatment
- selective mutism.

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified

6-year surveillance summary
Three studies were found about features of differential diagnoses for autism:

- There was disagreement between parent report and structured observation about indicative features of ASD and Reactive Attachment Disorder (RAD). It was concluded that the standardised measures might not be able to differentiate between RAD and ASD when differences are subtle (study type not specified in abstract)[199].
- Participants with ASD had a greater impairment in communication and social interaction (measured with the ADOS) compared to participants with ADHD and without diagnosis. It was concluded that ADOS could be used to differentiate between ASD and ADHD (study type not specified in abstract)[200].
- Motor dysfunction was common to both ASD and ADHD, but imitation deficits were specific to ASD (study type not specified in abstract)[201].

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
New evidence was found about indicative features of RAD and ADHD to differentiate from ASD which are already included in Appendix K of the full guideline providing advice to support the process of differentiating between alternative diagnoses with similar features. Imitation deficits are not listed in Appendix K but new evidence comes from a very small study. It was considered that additional consistent evidence would be needed before considering further differential features of autism for inclusion in the guideline.

New evidence is unlikely to change guideline recommendations.

Diagnostic assessment

Local pathway for recognition, referral and diagnostic assessment of possible autism

Autism diagnostic assessment for children and young people

After the autism diagnostic assessment

128 – 05 How should information be integrated to arrive at diagnosis?

Subquestion

a) Is the diagnostic assessment more accurate and reliable when performed by a multidisciplinary team or a single practitioner?

Recommendations derived from this question

1.1.1 A local autism multi-agency strategy group should be set up, with managerial, commissioner and clinical representation from child health and mental health services, education, social care, parent and carer service users, and the voluntary sector.

1.1.2 The local autism strategy group should appoint a lead professional to be responsible for the local autism pathway for recognition, referral and diagnosis of children and young people. The aims of the group should include:

- improving early recognition of autism by raising awareness of the signs and symptoms of autism through multi-agency training (see tables 1–3 in appendix C)
- making sure the relevant professionals (healthcare, social care, education and voluntary sector) are aware of the local autism pathway and how to access diagnostic services
- supporting the smooth transition to adult services for young people going through the diagnostic pathway
- ensuring data collection and audit of the pathway takes place.

1.1.3 In each area a multidisciplinary group (the autism team) should be set up. The core membership should include a:

- paediatrician and/or child and adolescent psychiatrist
- speech and language therapist
- clinical and/or educational psychologist.

1.1.4 The autism team should either include or have regular access to the following professionals if they are not already in the team:

- paediatrician or paediatric neurologist
- child and adolescent psychiatrist
- educational psychologist
- clinical psychologist
- occupational therapist.

1.1.5 Consider including in the autism team (or arranging access for the team to) other relevant professionals who may be able to contribute to the autism diagnostic assessment. For example, a specialist health visitor or nurse, specialist teacher or social worker.

1.1.6 The autism team should have the skills and competencies to:

- carry out an autism diagnostic assessment
- communicate with children and young people with suspected or known autism, and with their parents and carers, and sensitively share the diagnosis with them.

1.1.7 Autism team members should:

- provide advice to professionals about whether to refer children and young people for autism diagnostic assessments
- decide on the assessment needs of those referred or when referral to another service will be needed
- carry out the autism diagnostic assessment
- share the outcome of the autism diagnostic assessment with parents and carers, and with children and young people if appropriate
- with parent or carer consent and, if appropriate, the consent of the child or young person, share information from the autism diagnostic assessment directly with relevant services, for example through a school visit by an autism team member
- offer information to children, young people and parents and carers about appropriate services and support.

1.1.8 Provide a single point of referral for access to the autism team.

1.1.9 The autism team should either have the skills (or have access to professionals that have the skills) needed to carry out an autism diagnostic assessment, for children and young people with special circumstances including:

- coexisting conditions such as severe visual and hearing impairments, motor disorders including cerebral palsy, severe intellectual disability, complex language disorders or complex mental health disorders
- looked-after children and young people.

1.1.10 If young people present at the time of transition to adult services, the autism team should consider carrying out the autism diagnostic assessment jointly with the adult autism team, regardless of the young person's intellectual ability.

1.5.5 Include in every autism diagnostic assessment:

- detailed questions about parent's or carer's concerns and, if appropriate, the child's or young person's concerns
- details of the child's or young person's experiences of home life, education and social care
- a developmental history, focusing on developmental and behavioural features consistent with ICD-10 or DSM-IV criteria (consider using an autism-specific tool to gather this information)
- assessment (through interaction with and observation of the child or young person) of social and communication skills and behaviours, focusing on features consistent with ICD-10 or DSM-IV criteria (consider using an autism-specific tool to gather this information)
- a medical history, including prenatal, perinatal and family history, and past and current health conditions
- a physical examination
- consideration of the differential diagnosis (see recommendation 1.5.7)
- systematic assessment for conditions that may coexist with autism (see recommendation 1.5.15)
- development of a profile of the child's or young person's strengths, skills, impairments and needs that can be used to create a needs-based management plan, taking into account family and educational context.
- communication of assessment findings to the parent or carer and, if appropriate, the child or young person.

1.5.6 Perform a general physical examination and look specifically for:

- skin stigmata of neurofibromatosis or tuberous sclerosis using a Wood's light
- signs of injury, for example self-harm* or child maltreatment**
- congenital anomalies and dysmorphic features including macrocephaly or microcephaly.

1.5.8 Consider which assessments are needed to construct a profile for each child or young person, for example:

- intellectual ability and learning style
- academic skills
- speech, language and communication
- fine and gross motor skills
- adaptive behaviour (including self-help skills)
- mental and emotional health (including self-esteem)
- physical health and nutrition
- sensory sensitivities

- behaviour likely to affect day-to-day functioning and social participation
- socialisation skills.

1.5.10 Use information from all sources, together with clinical judgment, to diagnose autism based on ICD-10 or DSM-IV criteria.

1.5.12 Be aware that in some children and young people there may be uncertainty about the diagnosis of autism, particularly in:

- children younger than 24 months
- children or young people with a developmental age of less than 18 months
- children or young people for whom there is a lack of available information about their early life (for example some looked-after or adopted children)
- older teenagers
- children or young people with a complex coexisting mental health disorder (for example ADHD, conduct disorder, a possible attachment disorder), sensory impairment (for example severe hearing or visual impairment), or a motor disorder such as cerebral palsy.

1.5.13 Be aware that some children and young people will have features of behaviour that are seen in the autism spectrum but do not reach the ICD-10 or DSM-IV diagnostic criteria for definitive diagnosis. Based on their profile, consider referring to appropriate services.

1.5.14 If the outcome of the autism diagnostic assessment clearly indicates that the child or young person does not have autism, consider referring them to appropriate services based on their profile.

1.5.16 Be aware that in children and young people with communication difficulties it may be difficult to recognise functional problems or mental health problems.

1.6.3 During the autism diagnostic assessment, consider any potential risk of harm to, and from, the child or young person and take appropriate action.

* See 'Self-harm: the short-term physical and psychological management and secondary prevention of self-harm in primary and secondary care' (NICE clinical guideline 16).

** See 'When to suspect child maltreatment' (NICE clinical guideline 89).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Subquestion

b) What is the stability of an autism diagnosis over time?

Recommendations derived from this question

1.5.10 Use information from all sources, together with clinical judgment, to diagnose autism based on ICD-10 or DSM-IV criteria.

Surveillance decision

This review question should not be updated.

2-year evidence update summary

Two studies were found relating to the stability of a diagnosis of autism over time:

- A cohort study[202] assessed symptoms of autism over time in children with possible autism (n=65) compared with a control group (n=13). After the final visit, 39 children were diagnosed with autism, 20 with typical development, and 19 with other diagnoses. Further analysis resulted in 4 classes of autism: 21% severe persistent, 21% worsening, 19% improving and 40% non-spectrum.
- A systematic review[203] found that the proportion of children that still had a diagnosis at follow-up varied across the studies from 53 to 100%. There was also variability in the proportion of children that had moved from a diagnosis of autism to another autism spectrum disorder or moved off the spectrum completely.

4-year surveillance summary
No relevant evidence was identified.

6-year surveillance summary
No relevant evidence was identified.

Topic expert feedback

A topic expert referred to a study[204] (n=207 children) reporting re-evaluation of ASD diagnosis after two years of initial diagnosis (age 2 compared to age 4). At age 4, 80% of children retained an ASD diagnosis and 9% showed 'optimal progress'. Optimal progress was described as unclear ASD diagnosis as well as average skills of cognition, language and communication.

Impact statement
During the 2-year evidence update, it was concluded that the evidence relating to stability of the diagnosis over time suggested that children may show different symptoms of autism that could change their diagnosis. This supported the current recommendation which states that a child or young person should remain under review if there is uncertainty about the diagnosis.

New evidence is unlikely to change guideline recommendations.

Subquestion

c) What is the agreement of an autism diagnosis across different diagnostic tools?

Recommendations derived from this question

No recommendation made in the guideline

During guideline development, it was apparent that evidence on the accuracy of diagnostic tools was of very low quality. For that reason, evidence comparing the agreement between tools was not examined and no recommendations were made.

Surveillance decision

This review question should be updated.

2-year evidence update summary
Two studies were found reporting sensitivity and specificity with DSM-IV-TR and DSM-5:

- In children with intellectual disabilities, sensitivity of DSM-IV-TR criteria for diagnosing autism ranged from 33% to 74% and specificity ranged from 45% to 88% (study type not specified in abstract)[205].
- DSM-5 criteria had lower sensitivity than DSM-IV-TR (0.81 vs 0.95 respectively) but better specificity (0.97 vs 0.86 respectively). Reducing symptom criteria by 1 gave DSM-5 an increased sensitivity of 0.93 and specificity of 0.95 (study type not specified in abstract)[206].

During the evidence update, it was concluded that the evidence suggest the criteria for diagnosis of autism in DSM-5 result in broadly similar diagnoses of autism to those in DSM-IV-TR, so have no effect on current recommendations.

4-year surveillance summary

Eight studies were identified relating to the new DSM-5 as diagnostic criteria for ASD:

- Participants who met DSM-IV criteria for a pervasive developmental disorder (PDDs), only 57.1% met DSM-5 criteria (study type not specified in abstract)[207].
- In children previously diagnosed with either Autistic Disorder or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), 63% met the new DSM-5 criteria including 81% previously diagnosed with Autistic Disorder, however, only 17% of those with PDD-NOS met the new criteria (study type not specified in abstract)[208].
- Children classified as having ASD based on the DSM-IV criteria, 81.2% of the group met the new DSM-5 criteria (study type not specified in abstract)[209].
- 36% of participants with ASD with DSM-IV-TR would no longer meet the criteria under the proposed DSM-5 (study type not specified in abstract)[210].
- In children with DSM-IV clinical PDD diagnoses, the proposed DSM-5 criteria identified 91% children. DSM-5 had a specificity of 0.53 overall which increased to 0.63 based on data from both parent and clinical observation (study type not specified in abstract)[211].
- Agreement between the Childhood Autism Rating Scale (CARS) and Checklist for Autism Spectrum Disorder (CASD) and DSM-5 was 84% and 88% respectively and 94% between CARS and CASD (study type not specified in abstract)[212].
- Agreement between DSM-5, DSM-IV, and CASD was reported with sensitivity for low and high functioning autism at 98% for DSM-5 and 100% for DSM-IV. However, only 27% of children with pervasive developmental disorder not otherwise specified were identified by DSM-5 as having ASD (study type not specified in abstract)[213].
- Using data from the Autism Diagnostic Observation Schedule (ADOS) only 33% of participants fulfilled DSM-5 criteria compared to 83% when using the Autism Diagnostic Interview-Revised (ADI-R). However, 93% of participants met DSM-5 criteria when using combined data from both tools (study type not specified in abstract)[214].

6-year surveillance summary

Three studies were found reporting the proportion of children retaining their diagnosis with DSM-5 who were first diagnosed with DSM-IV-TR:

- Fulfilment of DSM-5 impairment criterion at 3 different levels: mild level 88%, moderate level 69%, and severe level 33% (study type not specified in abstract)[215].
- Between 50 and 75% of individuals maintained ASD diagnosis (systematic review [included studies were not specified in abstract])[216].
- Decrease in three diagnoses: ASD (31%), Autistic disorder (22%) and pervasive developmental disorder-not otherwise specified (70%) (systematic review and meta-analysis [included studies were not specified in abstract])[217].

Topic expert feedback

During the 4-year surveillance review, topic experts highlighted the updated version of the international classification system Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-5).

During the 6-year surveillance review, topic experts highlighted that DSM-5 includes a revision of the diagnostic criteria for ASD. The revisions of DSM-5 might also have a considerable impact (in line with CG128) about the importance of considering co-morbidities and co-occurring conditions. The new framework of DSM-5 appears to remove the emphasis on language delay and age of onset; the three areas of impairments in ASD have been reduced to two and the clinical specifiers of ASD in the individual are described in more detail.

Impact statement

At the 4-year surveillance review it was considered that there was variable evidence showing agreement across the different tools. In the original guideline, the Guideline Committee did not consider any evidence comparing agreement between diagnostic tools due to the low quality of evidence relating to accuracy. Due to heterogeneity between studies, it was felt unlikely that there was sufficient evidence to make any recommendations in this area.

This cumulative evidence identified through the surveillance showed that a diagnosis of ASD is less common with DSM-5 than with DSM-IV or DSM-IV-TR. The current guidance refers to DSM-IV as one of the diagnostic assessments. However, the DSM-IV was updated in 2013 and the new version (DSM-5) supersedes DSM-IV. Therefore, this evidence may have an impact on recommendations 1.5.5, 1.5.10, and 1.5.13 which refer to the DSM-IV criteria.

New evidence identified that may change current recommendations.

Diagnostic assessment

Autism diagnostic assessment for children and young people

Communicating the results from the autism diagnostic assessment

128 – 06 How should the findings of the diagnostic assessment be communicated to children and young people, and their families/carers?

Recommendations derived from this question

1.5.4 Discuss with the parents or carers and, if appropriate, the child or young person, how information should be shared throughout the autism diagnostic assessment, including communicating the outcome of the assessment. Take into account, for example, the child or young person's age and ability to understand.

1.8.1 After the autism diagnostic assessment discuss the findings, including the profile, sensitively, in person and without delay with the parents or carers and, if appropriate, the child or young person. Explain the basis of conclusions even if the diagnosis of autism was not reached.

1.8.2 Use recognised good practice when sharing a diagnosis with parents, carers, children and young people.

1.8.3 For children and young people with a diagnosis of autism, discuss and share information with parents or carers and, if appropriate, the child or young person, to explain:

- what autism is
- how autism is likely to affect the child or young person's development and function.

1.8.4 Provide parents or carers and, if appropriate, the child or young person, with a written report of the autism diagnostic assessment. This should explain the findings of the assessment and the reasons for the conclusions drawn.

1.8.5 Share information, including the written report of the diagnostic assessment, with the GP.

1.8.6 With parental or carer consent and, if appropriate, the consent of the child or young person, share information with key professionals involved in the child's or young person's care, including those in education and social care.

1.8.8 For children and young people with a diagnosis of autism, offer a follow-up appointment with an appropriate member of the autism team within 6 weeks of the end of the autism assessment for further discussion (for example about the conclusions of the assessment and the implications for the child or young person).

1.8.9 For children and young people with a diagnosis of autism, discuss with parents or carers the risk of autism occurring in siblings and future children.

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
No relevant evidence was identified

6-year surveillance summary
No relevant evidence was identified

Topic expert feedback
Topic experts referred the following studies:

- A study[218] reported parents' experience (from a survey) about the process of attaining a diagnosis of ASD for their children. Over half of parents were dissatisfied with the diagnosis process. One of the factors predicting parents' satisfaction was related to the information provided at diagnosis.
- A qualitative study[219] explored parents' experience with a 'feedback session' related to the diagnosis of ASD. Parents reported issues related to the structure, style and content of the session.

Impact statement
New evidence was found about parents' experience during the ASD diagnosis process. Although information was a predictor of parents' satisfaction with the diagnosis process, it was not clear how and what information was provided. Therefore, this new evidence is unlikely to change current recommendations which already suggest discussing the findings of diagnostic assessment to parents and carers, and if appropriate, the child or young person without delay, and give recommendations on how this information should be delivered.

New evidence is unlikely to change guideline recommendations.

Diagnostic assessment

Autism diagnostic assessment for children and young people

After the autism diagnostic assessment

128 – 07 What actions should follow assessment for children and young people who are not immediately diagnosed with autism?

Recommendations derived from this question

1.5.9 If there are discrepancies during the autism diagnostic assessment between reported signs or symptoms and the findings of the autism observation in the clinical setting, consider:

- gathering additional information from other sources and/or
- carrying out further autism-specific observations in different settings, such as the school, nursery, other social setting or at home.

1.6.1 If there is uncertainty after the autism diagnostic assessment about the diagnosis, consider keeping the child or young person under review, taking into account any new information.

1.6.2 If any of the following apply after assessment, consider obtaining a second opinion (including referral to a specialised tertiary autism team if necessary):

- continued uncertainty about the diagnosis
- disagreement about the diagnosis within the autism team
- disagreement with parents or carers or, if appropriate, the child or young person, about the diagnosis
- a lack of local access to particular skills and competencies needed to reach a diagnosis in a child or young person who has a complex coexisting condition, such as a severe sensory or motor impairment or mental health problem
- a lack of response as expected to any therapeutic interventions provided to the child or young person.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Assessment of coexisting conditions

Autism diagnostic assessment for children and young people

128 – 08 Which are the common coexisting conditions that should be considered as part of assessment?

Subquestion

- neurodevelopmental: speech and language problems, intellectual disability, coordination, learning difficulties in numeracy and literacy.

Recommendations derived from this question

1.5.15 Consider whether the child or young person may have any of the following as a coexisting condition, and if suspected carry out appropriate assessments and referrals:

- Mental and behaviour problems and disorders:
  - ADHD
  - anxiety disorders and phobias
  - mood disorders
  - oppositional defiant behaviour
  - tics or Tourette syndrome
  - OCD
  - self-injurious behaviour.
- Neurodevelopmental problems and disorders:
  - global delay or intellectual disability
  - motor coordination problems or DCD
  - academic learning problems, for example in literacy or numeracy
  - speech and language disorder.
- Medical or genetic problems and disorders:
  - epilepsy and epileptic encephalopathy
  - chromosome disorders
  - genetic abnormalities, including fragile X
  - tuberous sclerosis
  - muscular dystrophy
  - neurofibromatosis.
- Functional problems and disorders:
  - feeding problems, including restricted diets
  - urinary incontinence or enuresis

- constipation, altered bowel habit, faecal incontinence or encopresis
- sleep disturbances
- vision or hearing impairment.

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
Two studies were found reporting on neurodevelopmental coexisting conditions of autism:

- A study reported that 100 of 129 children met the criteria for ASD, of which 36% had an intellectual developmental disorder, 56% had language disorder, 37% had hyperactivity, and 7% had epilepsy (study type not specified in abstract)[220].
- Regression of language, social skills and cognition were important characteristics of a regression-autistic group compared to children with ASD and no reported regression (study type not specified in abstract)[221].

6-year surveillance summary
No relevant evidence was identified.

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement
At the 4-year surveillance review it was considered that the evidence relating to co-existing neurodevelopmental conditions, including intellectual disability and language disorder, was consistent with the conditions identified in the guideline. No new evidence was identified at the 6-year surveillance review to change this conclusion.

New evidence is unlikely to change guideline recommendations.

Subquestion

- mental and behavioural disorders, such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety, depression, Tourette, tic disorders.

Recommendations derived from this question

1.5.15 Consider whether the child or young person may have any of the following as a coexisting condition, and if suspected carry out appropriate assessments and referrals:

- Mental and behaviour problems and disorders:
  - ADHD
  - anxiety disorders and phobias
  - mood disorders
  - oppositional defiant behaviour
  - tics or Tourette syndrome
  - OCD
  - self-injurious behaviour.
- Neurodevelopmental problems and disorders:
  - global delay or intellectual disability
  - motor coordination problems or DCD

  - academic learning problems, for example in literacy or numeracy
  - speech and language disorder.
- Medical or genetic problems and disorders:
  - epilepsy and epileptic encephalopathy
  - chromosome disorders
  - genetic abnormalities, including fragile X
  - tuberous sclerosis
  - muscular dystrophy
  - neurofibromatosis.
- Functional problems and disorders:
  - feeding problems, including restricted diets
  - urinary incontinence or enuresis
  - constipation, altered bowel habit, faecal incontinence or encopresis
  - sleep disturbances
  - vision or hearing impairment.

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
Three studies were found reporting on metal and behavioural disorders as coexisting conditions of autism:

- A study found that the most common conditions were attention-deficit/hyperactivity disorder, oppositional defiant disorder and anxiety disorder (study type not specified in abstract)[222].
- A study of the clinical characteristics of high functioning young people with an ASD and anxiety found that the most common anxiety disorders in the group were social phobia and generalised anxiety disorder. 92% of participants also had two or more types of anxiety disorder (study type not specified in abstract)[223].
- A study examining the comorbidity of bipolar disorder and autism spectrum disorders in young people found that 30% of participants with bipolar I disorder met the criteria for ASD (study type not specified in abstract)[224].

During the 4-year surveillance review, it was concluded that the evidence relating to co-existing mental and behavioural conditions, including ADHD and anxiety disorders was consistent with the conditions identified in the guideline.

6-year surveillance summary
Three studies reported the prevalence of mental and behavioural disorders in children and adolescents with autism:

- mood disorder (5%)[225]
- depression (37%)[226]
- attention deficit hyperactivity disorder (49%)[226] and (59.1%)[227]
- oppositional defiant disorder (45%)[226]
- generalised anxiety disorder (66.5%)[227]
- specific phobias (52.7%)[227]

None of these studies compared the prevalence of mental and behavioural disorders between children and adolescents with and without autism (study type not specified in abstract).

Topic expert feedback
No topic expert feedback was relevant to this evidence.

Impact statement

Through surveillance, it was found that ADHD, anxiety disorders and phobias, mood disorders, and oppositional defiant behaviour were coexisting conditions as identified in the guideline. However, none of these studies provided evidence on any of the following criteria that the Guideline Committee agreed for a disease or symptom to be considered a coexisting condition with autism:

- higher prevalence rate than that for general population
- likely to benefit from appropriate interventions
- likely to have an important impact on quality of life.

New evidence is unlikely to change guideline recommendations.

Subquestion

- medical or neurological problems such as functional gastrointestinal problems, tuberous sclerosis, neurofibromatosis.

Recommendations derived from this question

1.5.15 Consider whether the child or young person may have any of the following as a coexisting condition, and if suspected carry out appropriate assessments and referrals:

- Mental and behaviour problems and disorders:
  - ADHD
  - anxiety disorders and phobias
  - mood disorders
  - oppositional defiant behaviour
  - tics or Tourette syndrome
  - OCD
  - self-injurious behaviour.
- Neurodevelopmental problems and disorders:
  - global delay or intellectual disability
  - motor coordination problems or DCD
  - academic learning problems, for example in literacy or numeracy
  - speech and language disorder.
- Medical or genetic problems and disorders:
  - epilepsy and epileptic encephalopathy
  - chromosome disorders
  - genetic abnormalities, including fragile X
  - tuberous sclerosis
  - muscular dystrophy
  - neurofibromatosis.
- Functional problems and disorders:
  - feeding problems, including restricted diets
  - urinary incontinence or enuresis
  - constipation, altered bowel habit, faecal incontinence or encopresis

- sleep disturbances
- vision or hearing impairment.

Surveillance decision

This review question should not be updated.

2-year evidence update summary
No relevant evidence was identified.

4-year surveillance summary
Twenty-three studies were found reporting on medical or neurological coexisting conditions of autism:

- An association was found between autistic regression and febrile seizures and a family history of neuropsychiatric disorders (study type not specified in abstract)[228].
- Prevalence of autistic regression and minor neurological and musculoskeletal deficits were higher in females than males with ASD (study type not specified in abstract)[229].
- Iron deficiency in children with ASD may be more common than in the general population (retrospective study)[230].
- Iron deficiency anaemia (IDA) increased the risk of psychiatric disorders, including autism spectrum disorder (study type not specified in abstract)[231].
- There was 14.1% prevalence of ASD in a group of children with a neurological disorder (study type not specified in abstract)[232].
- 33.3% of autistic children had epilepsy (study type not specified in abstract)[233].
- In people with Asperger's syndrome, 3.9% were registered with at least one epilepsy diagnosis compared to a general population estimate of 2% (retrospective study)[234].
- Average prevalence of epilepsy in children with ASD was 12.5% (study type not specified in abstract)[235].
- 37% of children with epilepsy were screened positive for autism (study type not specified in abstract)[236].
- 46% of children and adolescents with ASD had a comorbid disorder, in particular, epilepsy (10.1%), ADHD (18%) and an anxiety disorder (15.7%) (study type not specified in abstract)[237].
- Around 6-7% of children with vision impairment or hearing loss had co-occurring ASD (study type not specified in abstract)[238].
- 40% of children with autism or a related disorder had an ophthalmic abnormality, including significant refractive errors (29%), strabismus (21%) and amblyopia (10%) (study type not specified in abstract)[239].
- 52% of children with an ASD were found to have an ocular abnormality (study type not specified in abstract)[240].
- 29% of children presenting with functional defecation disorders at a specialised outpatient clinic had co-occurring ASD symptoms (study type not specified in abstract)[241].
- Frequent gastrointestinal symptoms were more common in children with ASD or developmental delay (DD) compared to typically developing children (study type not specified in abstract)[242].
- Individuals with a positive coeliac disease serologic test result had an increased risk for later diagnosis of an ASD (study type not specified in abstract)[243].
- Functional constipation was the most common type of gastrointestinal dysfunction in children with ASD (85.0%) (study type not specified in abstract)[244].
- There was no increased risk of small intestine permeability associated with autism spectrum disorders (study type not specified in abstract)[245].
- People with Asperger's syndrome have an increased risk of cerebral palsy relative to the general population (study type not specified in abstract)[246].
- Frequency of co-occurring ASD with cerebral palsy was 6.9%, with 18.4%

frequency in non-spastic cerebral palsy (study type not specified in abstract)[247].

- Participants with ASDs had an increased risk of asthma, allergic rhinitis, atopic dermatitis, urticaria, and type 1 diabetes (study type not specified in abstract)[248].
- There was an increased risk of autism spectrum disorder in people with Klinefelter syndrome (study type not specified in abstract)[249].
- A number of co-existing conditions were reported by individuals with ASD including eating disorders (94%), obsessive-compulsive behaviours (92%), behavioural problems (89%), and sensory processing problems (85%) (study type not specified in abstract)[250].

During the 4-year surveillance, it was concluded that new evidence was unlikely to impact on current guideline recommendations because the majority of studies identified through the literature search relate to conditions described in the current guidance.

6-year surveillance summary

Eight studies were found reporting on medical or neurological coexisting conditions of autism:

- Higher prevalence of gastrointestinal symptoms in children with ASD compared to children without ASD (a meta-analysis and a cohort study)[251,252].
- Prevalence of gastrointestinal symptoms in children with high-functioning autism was 61% (study type not specified in abstract)[253].
- Higher prevalence of overweight and obesity in children and adolescents with autism compared to children without autism (reference 251 is a survey, study type not specified in abstract for references 252-253)[254-256].
- Prevalence of overweight and obesity was 18.1% and 17.0%, respectively in children with ASD (study type not specified in abstract)[257].
- Ophthalmic pathology in children with ASD was 26.9 % (retrospective study)[258].

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

Through surveillance, medical and functional problems were found to be coexisting conditions as identified in the guideline. Five of these 31 studies provided evidence on one of the criteria that the Guideline Committee agreed for a disease or symptom to be considered a coexisting condition with autism:

- higher prevalence rate than that for general population.

However, none of the studies provided evidence on the other 2 criteria:

- likely to benefit from appropriate interventions
- likely to have an important impact on quality of life.

New evidence is unlikely to change guideline recommendations.

Information and support

Information and support for families and carers

128 – 09 What information do children and young people, and their families/carers, need during the process of referral, assessment and diagnosis of autism?

Recommendations derived from this question

1.9.1 Provide individual information on support available locally for parents, carers, children and young people with autism, according to the family's needs. This may include:

- contact details for:

  - local and national support organisations (who may provide, for example, an opportunity to meet other families with experience of autism, or information about specific courses for parents and carers and/or young people)
  - organisations that can provide advice on welfare benefits
  - organisations that can provide information on educational support and social care
- information to help prepare for the future, for example transition to adult services

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Information and support

Information and support for families and carers

128 – 10	**What kinds of day-to-day, ongoing support (not specific to therapeutic interventions/management of autism) should be offered to children and young people, and their families/carers, during the process of referral, assessment and discussion of diagnosis of autism?**

Recommendations derived from this question

Recommendation 1.9.1 (see listed above for question 128-09).

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the NICE database for research recommendations. The research recommendations will remain in the full versions of the guideline. See NICE's research recommendations process and methods guide 2015 for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 6-year surveillance review time point a decision **will not** be taken on whether to retain the research recommendations or stand them down.

RR – 01 Does training professionals to recognise signs and symptoms of autism lead to earlier assessment of needs and earlier diagnosis (and by implication reduce morbidity/improve health outcomes) among children and young people with suspected autism compared with no training?

New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.

During the 4-year surveillance review, a study[259] was identified which aimed to assess the effectiveness of a training programme on rates of diagnostic identification of autism spectrum disorder within a community paediatric setting. Twenty-seven paediatric providers participated in the training programme over a 3.5 year period. The findings indicated that there was an 85% increase in identification of children with autism spectrum disorder following training.

The evidence was insufficient to answer the research recommendation on training to improve recognition of autism in children and young people. The abstract provides no information to suggest any comparisons were made with clinical services where the additional training was not available. Nor is there any information regarding effectiveness in terms of age, time between parents' concerns and autism diagnosis, impact on under-diagnosed groups and earlier referral rates.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 02 Does routine additional information from educational settings (such as nursery or school) improve accuracy in diagnosing autism among children or young people up to the age of 19 compared with signs and symptoms alone?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 03 Do additional assessments (for IQ, language ability and motor ability) improve accuracy in diagnosing autism among preschool children (younger than 5 years) compared with signs and symptoms alone?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 04 What is the effectiveness and acceptability of comparative genomic hybridisation (CGH) array compared with current genetic testing in children and young people with identified autism?

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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