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Centre for Clinical Practice – Surveillance Programme

Surveillance review consultation document

4-year surveillance review of CG128: Autism: recognition, referral and diagnosis of children and young people on the autism spectrum

Background information

Guideline issue date: September 2011
4-year review: 2014

Surveillance review recommendation

Surveillance review proposal put to consultees:

The Autism in children and young people guideline should not be considered for an update at this time.

Main findings of the current 4 year surveillance review

An Evidence Update was produced for the guideline in 2013 and was used as a source of evidence for the review proposal. The Evidence Update indicated that there is currently insufficient new evidence to invalidate the guideline recommendations. For the 4 year Surveillance Review, a search to identify new evidence was carried out for articles published between 29th October 2012 (the end of the search period for the Evidence Update) and 29th January 2014 and relevant abstracts were assessed. As a diagnostic guideline, the search strategy included observational studies in addition to randomised clinical trials (RCTs) and systematic reviews. Clinical feedback was also obtained from members of the guideline development group (GDG) through a questionnaire survey.

New evidence was identified for the current 4 year surveillance review relating to the following clinical areas within the guideline.

Clinical area: Recognition		
Q: What are the signs and symptoms that should prompt a healthcare professional or other professional in any context to think of autism?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update One study[1] (n=86), a retrospective analysis of data from a cohort study examined early predictors (up to age 30 months) of later autism (up to age 11 years). At age 6 months, differences in fine motor skills and social skills and communication, and concerns about vision were associated with subsequent diagnosis of autism. Differences in hearing, vocabulary and understanding words, and in feeding difficulties and fads were apparent by age 15 months. At age 18 months, more widespread differences were associated with a subsequent diagnosis of autism: listening and responding to sounds, play and imitation, health concerns and repetitive and unusual behaviours. Temperamental traits and differences in bowel habit and stool characteristics were noticed by age 24 months, and by 30 months differences in crying and tempers were associated with autism. Two studies compared differences in behavioural features of autism spectrum disorders (ASDs) between boys and girls. A study[2] (n=325) examining the female phenotype of autism found that girls had less repetitive stereotyped behaviour, fine-motor impairment and lower hyperactivity and inattention than boys. However, girls were reported to have a higher level of emotional problems and prosocial behaviour. A second study[3] (n=2568) reported that girls with ASDs were less likely than boys to show aggressive behaviour or hyperactivity or short attention span but were more likely to have	None identified.	The new evidence on signs and symptoms is broadly consistent with the signs and symptoms of possible autism listed within the guideline. One exception is a study which suggested that head lag in children is linked with ASD. However, as a small study it is unlikely that this would provide sufficient evidence to change the guideline recommendations. Furthermore, the guideline recommends that autism should not be ruled out if the exact signs and symptoms described in the guideline are not evident. Two studies were identified in the Evidence Update which suggested that differences in symptoms of autism may exist between girls and boys which could contribute to under-recognition of autism in girls, which was an issue identified in the guideline. The evidence from the two studies is heterogeneous in relation to the differences between boys and girls, and as the guideline already recommends that when considering the possibility of autism practitioners should be aware that autism may be under-diagnosed in girls, it is unlikely that this evidence would impact on current guideline recommendations.

seizures or seizure-like behaviour. A study[4] (n=2720) investigating differences in children with three different patterns of autism symptom onset (regression, plateau, and no loss/plateau) was identified. The results indicated 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. A study[5] including a mixed group of children with autism and of typical development (n=75) examined levels of social communication behaviours at ages 6–24 months. 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. By 24 months all children with autism had significantly lower social-communication behaviour than typically developing children. **4-year surveillance review (2014)** Pre-school children (0–5 years) An observational study[6] was identified which aimed to assess the association between head lag during pull-to-sit at age 6 months and autism risk status. 40 infant siblings of children with autism were studied prospectively from 6 to 36 months and then assessed for autism. The results were then compared with a new group of 20 high-risk and 21 low-risk infants. The findings suggest that head lag at 36 months is linked with autism spectrum disorder, particularly in high risk infants.		

<u>Primary school age</u> One study[7] was identified which 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. <u>Mixed age groups</u> Three studies were identified in mixed age groups. One study[8] was identified which examined the fine and gross motor performance of children with ASD using the Movement Assessment Battery for Children-2 (MABC-2). The results suggested that the majority of children with autism experienced motor difficulty or were at risk for motor delay when compared to age-matched typically developing children. Another study[9] (n=62) reported that anger is commonly experienced by young people with Asperger's syndrome (AS) and that there is a positive correlation between anger and anxiety and depression. One study[10] including 95 children examined the clinical features and comorbidities of AS. The key clinical features included poor communication skills (95%) and repetitive and stereotyped patterns of behaviour (77%), and comorbidities included attention deficit hyperactivity disorder (39%) and emotional disorder (18%).		
Clinical area: Following referral		
Q: Are there tools to identify an increased likelihood of autism that are effective in assessing the need for specialist autism assessment?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update</u>	One GDG member reported that there is more evidence on screening tools but it is unlikely to	A number of different tools to identify an increased likelihood of autism were identified in the new

Manchester Inventory for Playground Observation (MIPO) One study[11] was identified which investigated the reliability and validity of the Manchester Inventory for Playground Observation (MIPO) tool in children with autism spectrum disorders and with other emotional or behavioural difficulties. The tool was able to discriminate between cases and controls with a sensitivity of 0.75 and specificity of 0.88, and there was a classification accuracy of 69% for autism spectrum disorders. SSI A study[12] of the validity of the screen for social interaction (SSI) as a screening tool for ASDs was identified. 350 children with ASDs, PDD-NOS and no developmental concerns were included in the study. The SSI differentiated between each of the diagnostic groups. Further refinement of the SSI resulted in two separate tools for a younger age group (SSI-Y), with a positive predictive value of 0.87, and for an older age group (SSI-O), with a positive predictive value of 0.78. CSI-4 One study[13] assessed three separate Child Symptom Inventory-4 (CSI-4) scoring algorithms for differentiating between children with ASDs and children with ADHD. 186 children with autism and 251 children with ADHD were included in the study. At optimum cut-off scores for differentiating between autism and ADHD, the three algorithms produced sensitivities ranging from 0.84 to 0.91 and specificities of 0.72 to 0.96, with the second parent algorithm producing the highest predictive value. SCQ A study[14] investigating the use of the Social	change recommendations. No details of evidence were provided. Another GDG member said that there are several new studies examining the M-CHAT screening instrument which might need to be considered as part of the surveillance review. However, no details of studies were provided.	evidence, including six studies which examined the effectiveness of the M-CHAT. There was no consistent evidence across the studies which confirmed one tool as meeting the GDG's pre-defined acceptable level for predictive accuracy (sensitivity and specificity of at least 80%). The guideline recommended 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 but should not be used to make or rule out a diagnosis of autism. There remains insufficient, consistent evidence to recommend use of a specific tool that is able to identify an increased likelihood of autism and therefore, it is unlikely that the new evidence will impact on this recommendation.

Communication Questionnaire (SCQ) as a second-level screening tool in 208 children at high risk of ASD was identified. The results found that that for detecting autism, the SCQ had a sensitivity of 0.76 and specificity of 0.62, and for ASDs, a sensitivity of 0.66 and specificity of 0.62. **4-year surveillance review (2014)** Autism-spectrum quotient An observational study[15] (n=354) found that adolescents with Asperger syndrome and high-functioning autism scored significantly higher on the French version of the Autism Spectrum Quotient (AQ) compared to healthy controls and adolescents with psychiatric disorders. A cut-off score of 26 differentiated the autism group from healthy controls with 0.89 sensitivity and 0.98 specificity. Child Behaviour Checklist Two observational studies were identified which examined the use of the Child Behaviour Checklist for the identification of children with autism spectrum disorders. One study[16] (n=141) indicated that the Child Behaviour Check List 11/2-5 was able to discriminate children with ASD from children with other psychiatric disorders and typical development, with high sensitivity and specificity across sub-scales of the tool. A second study[17] assessed the combined use of the Child Behaviour Checklist and the Teacher's Report Form to identify children with ASDs. The study included children with ASD (n = 458), referred children without ASD (n=1109) and children from the general population (n = 999). The combined CBCL/TRF proved effective in identifying children with ASD, with high predictive		

values at a cut-off score of 8. POSI One study[18] reported on two trials which examined the reliability and validity of the Parent's Observations of Social Interactions (POSI), a seven-item screening instrument for autism spectrum disorders. In both studies, parents completed the POSI and the Modified Checklist for Autism in Toddlers (M-CHAT) checklist and scores were compared. Analysis of the results from both studies demonstrated that the POSI had comparable sensitivity and specificity to the M-CHAT with sensitivities of 89% and 83% and specificities of 54% and 75% for studies 1 and 2 respectively. SDQ Two studies[19,20] examining the diagnostic accuracy of the Strengths and Difficulties Questionnaire (SDQ) found that parent ratings for diagnosing children with ASD had a sensitivity of 66-79%, and specificity of 93%. M-CHAT Six studies were identified which reported mixed evidence of effectiveness of the Modified Checklist for Autism in Toddlers (M-CHAT): 3 studies[21-23] found that the M-CHAT is able to identify many cases of ASD in toddlers; 1 study[24] indicated that an electronic format of the tool reduced the number of false at-risk screens and false not-at-risk screens compared to paper format; 1 study[25] found that it was effective at identifying toddlers without ASD; and 1 study[26] suggested that the CHAT-23 was a more useful tool than the M-CHAT. PreAut Grid		

A study[27] examining the use of the PreAut grid in assessing the risk of autism in infants with West syndrome (WS) was identified. 25 patients with WS were assessed with the PreAut grid before 9 months followed by the checklist for autism in toddlers (CHAT) at 18 and 24 months. The results found that WS patients with a positive PreAut screening at 9 months had a significantly increased risk of having autism or intellectual disability at age 4 years compared to those with a negative screen. The Pre-Aut grid at 9 months demonstrated a similar diagnostic accuracy as the CHAT at both 18 and 24 months with sensitivity of 0.83 and specificity of 1. <u>TIDOS</u> One study[28] was identified which compared ratings on the Three-Item Direct Observation Screen (TIDOS) test for autism spectrum disorders completed by paediatric professionals with the Social Communication Questionnaire (SCQ) completed by parents. 86 children with a diagnosis of ASD, 76 with developmental delay without ASD, and 97 with typical development were included in the study. The results found that the SCQ had a sensitivity of 0.73 and specificity of 0.70. In comparison, the TIDOS had sensitivities ranging from 0.67 to 0.89 and specificities from 0.89 to 0.91 across the three-items included in the tool. The findings suggest that the tool has potential to improve screening for ASDs. <u>A-TAC Inventory</u> A study[29] was identified which examined the accuracy of the Autism-Tics, ADHD, and other Co-morbidities inventory (A-TAC) for predicting clinical diagnoses. At three-year follow-up of participants who had screened positive on the A-TAC for ASDs, 48% received a clinical diagnosis of ASDs.		

Toddler autism screening questionnaire A study[30] including 18 children with autism and of 59 typically developing children tested an 18-item screening questionnaire for generic autism in Taiwanese children. The results showed that the questionnaire had high sensitivity and specificity at cut-off scores of 5 and 6, suggesting its potential for identifying autism in Taiwanese children at risk for autism. SIQ A study[31] assessing a questionnaire to assess social development (SIQ) in preschool children was identified. Parents of 108 children with ASD, speech and language disorders, or 'developmental concerns' completed the SIQ and the Childhood Autism Rating Scale (CARS) assessment. Analysis of the results indicated that the SIQ was able to identify children positively diagnosed for autism on the CARS with a sensitivity of 85% and specificity of 85%. First Year Inventory A study[32] was identified which examined the ability of the First Year Inventory (FYI) to identify 12-month-old infants at risk of later diagnosis for autism spectrum disorder. As part of the study, parents of 699 children who had completed the FYI when their child was 12 months old completed additional screening questionnaires at age 3. Children who were found to be at risk for ASD were invited for in-person diagnostic evaluations. The results found that 31% of children identified as at risk for ASD at 12 months on the FYI received a confirmed diagnosis of ASD at 3 years old. A second study[33] examining the predictive validity of the FYI risk cutoffs was identified. Parents of		

613 12-month old infants completed the FYI. The results showed that the FYI identified 60% of those with ASD at 30 months follow-up. <u>SRS</u> A study[34] was identified which examined the ability of the parent-rated Social Responsiveness Scale (SRS) to differentiate between autism spectrum disorders and disruptive behaviour disorders. 55 children with ASD without comorbid intellectual delay, 55 with oppositional defiant/conduct disorder (ODD/CD) and 55 typically developing (TD) children were included in the study. The results showed that the SRS was able to differentiate between ASD and TD but did not perform as well when ASD was compared with ODD/CD. However, combining the score of the SRS with other parent-rated questionnaires improved its validity in differentiating between ASD and ODD/CD. One study[35] assessed the ability of the Spanish version of the Social Responsiveness Scale (SRS) to detect autism spectrum disorders (ASDs) in 200 children with a confirmed diagnosis of ASDs compared to a control group of 363 children without ASDs. The results indicated that the SRS is an effective screening tool for differentiating between children with ASDs and controls.		
Clinical area: Following referral		
Q: 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		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update</u> <u>Socioeconomic factors</u>	None identified.	It was the GDG's view that no risk factor in isolation necessitates a referral for an autism-specific diagnostic assessment, however, it is

A retrospective cohort study[36] investigated the individual and community-level factors that may affect the age of diagnosis of autism. 17,185 children with a diagnosis of autism were included in the study. Non-white ethnicity and poverty were associated with older age at diagnosis, and higher parental educational status and higher local property values were associated with lower age of diagnosis. Children with higher communication capabilities were also diagnosed at an older age. Familiar or parental factors A study[37] of 214 children with a previous diagnosis of autism spectrum disorder found that children of mothers with depression had higher scores on the Social Responsiveness Scale (SRS) compared with those whose mothers did not have depression. However, no differences were observed for ADI-R or ADOS scores. The authors concluded that depression in mothers may affect their reporting of symptoms of autism seen in their children. A retrospective secondary analysis[38] of a longitudinal UK cohort study investigated the impact of social and demographic factors on diagnosis of autism. 71 children with a diagnosis of autism and 142 controls were included in the analysis. About 9 times more boys than girls were diagnosed with autism. The mean age that mothers gave birth to children who were subsequently diagnosed with autism was higher than the age of the overall population. There was also an increased risk of autism in children who were born first compared to subsequent children. **4 year surveillance review (2014)** All factors		recommended that antenatal and perinatal history should be included as part of a referral. The risk factors identified in the new evidence were broadly consistent with the risk factors listed within the guideline. Other risk factors not identified in the guideline included: • Socioeconomic factors such as poverty and parental educational status; • Environmental factors such as air pollution; • Perinatal factors such as foetal growth and; • Pregnancy related factors such as maternal parity, interpregnancy interval, weight gain, high blood pressure, smoking, diet, hypothyroxinaemia, diabetes, fever, hormonal treatments and certain types of IVF treatment. However, additional consistent evidence would be needed before considering these new risk factors for inclusion in the guideline.

One study[39] (n=1,816) reported that male gender, low birth weight, low level of education of the mother, social, behavioural, language, psychomotor and eating problems were all predictors of ASD problems. <u>Familiar or parental factors</u> A Finnish case-control study[40], including 1132 cases and 4515 matched controls, found that there was an increased risk of childhood autism in Finnish second-generation migrants. The results of a systematic review and meta-analysis[41] (including 3 cohort studies and 9 case-control studies) showed a significant association between maternal diabetes and increased risk of autism in offspring. Two studies[42,43] found that that there was an increased risk of childhood autism with advancing paternal age. One cohort study[44] (n=4746) found that advancing parental age increases risk of ASDs, particularly for mothers aged 40-45 and fathers aged 55-59. A longitudinal cohort study[45] was identified which examined the impact of maternal exposure to childhood abuse on risk for ASD in offspring. The results indicated that there is a link between maternal exposure to abuse and risk of ASD in offspring, even once adverse perinatal factors have been accounted for. A case-control study[46] aiming to determine whether a family history of schizophrenia and/or bipolar disorder is a risk factor for ASDs was identified. The results showed that there is an increased risk for ASD in people who have a		

parent or sibling with schizophrenia. A study[47] was identified which aimed to determine whether risk for ASD is associated with maternal parity. The results suggest differences in association between maternal parity and ASD subtypes; for ASDs combined, there is a decreasing risk of autism with increasing parity; however, for childhood autism, the risk is increased for the second born child compared to the first. A cohort study[48] was identified which aimed to assess the relative recurrence risk for ASDs in a Danish population, including recurrence in full- and half-siblings. The results indicated that the relative recurrence risk for ASDs for maternal and paternal full-siblings were higher than the risks for half-siblings, suggesting that there is a genetic role in ASDs. <u>Perinatal or neonatal factors</u> A case-control study[49] (including 4713 cases and 4 matched controls per case) found that low birth weight, gestational age less than 32 weeks and small for gestational age were associated with increased risk of childhood autism. Five studies were identified which considered the association between pre-term birth and ASD risk. One study[50] (n=141) suggested that pre-term children display greater social-communication difficulties and autistic behaviour in early childhood than the general population. The results of 4 more studies[51-54] also found that there was an increased risk of ASD in pre-term children, with one study reporting an increased risk in infants born at 36 weeks or less, and another at 23-27 weeks gestation.		

A case-control study[55] including children aged 0-17 year was identified which aimed to examine the link between foetal growth and ASD. Analysis of the results indicated that there was an increased risk in ASD linked to foetal growth both below and above the mean for gestational age. A study[56] was identified which aimed to determine the link between neonatal cranial ultrasound abnormalities in low birth weight infants and ASD. Secondary analysis of the results found that any type of white matter injury significantly increased the risk of screening positive for ASD, with the greatest risk associated with ventricular enlargement. <u>Pregnancy-related factors</u> A case-control study[57] including 288 children was identified which aimed to examine the relationship between pre-, peri-, and neonatal factors and autism. Analysis of the results indicated the risk of autism was higher in children where mothers were taking medications and smoked during pregnancy. There were also significant links with neonatal dyspnea and congenital anomalies. A study[58] examining the link between interpregnancy interval and risk of autistic disorder was identified. 223,476 singleton full-sibling pairs were included in the study. The results of the study indicated that for interpregnancy intervals shorter than 12 months, there was an increased risk of autistic disorder in the second-born child. A study[59] was identified which found that childhood autism is linked with maternal high blood pressure, low Apgar scores (<7) and neonatal treatment with monitoring.		

Two studies investigated the link between ASD and maternal smoking in pregnancy. A case-control study[60] including 633,989 children indicated that there was no link between maternal smoking in pregnancy and ASD. However, the results of another case-control study[61] indicated that there was small increase in risk of pervasive developmental disorder associated with maternal smoking through the whole pregnancy. A study[62] was identified which found that low maternal intake of polyunsaturated fat before or during pregnancy was linked with an increased risk in ASD in offspring. The association between maternal use of prenatal folic acid supplements and subsequent risk of ASDs was examined in a prospective cohort study[63] of 85,176 children. The results indicated a slightly elevated risk of autistic disorder in children unexposed to folic acid compared to children of folic acid users. A study[64] examining the association between maternal autoimmune disease, asthma, and allergy with child ASD and developmental delay without autism (DD) found no association between maternal autoimmune disease and ASD alone. A case-control study[65] including 407 cases and 2,075 matched controls was identified which aimed to examine the link between maternal infections during pregnancy and risk of ASD. The study found no overall link between diagnoses of any maternal infection during pregnancy and ASD. However, there was an increased risk associated with infections diagnosed during a hospital admission and multiple infections during		

pregnancy. A study[66] assessing the relationship between maternal influenza or fever during pregnancy and ASD found that maternal fever during pregnancy led to an increased risk of ASD but that this risk was diminished in mothers who reported taking antipyretic medications. A study[67] which aimed to determine whether pre-pregnancy BMI and pregnancy weight gain are associated with increased autism spectrum disorder (ASD) risk was identified. The results indicated that three is an increased risk of ASD linked to pregnancy weight gain but that there is no link with pre-pregnancy BMI. A study[68] was identified which found that maternal use of valproate during pregnancy increases the risk of ASD and childhood autism in offspring. 3 studies reported on links between maternal antidepressant use and ASD risk. A case-control study[69] (n=4429) found that that there was significant link between maternal use of antidepressants during pregnancy and increased risk of ASD. However, one study[70] found no significant link between prenatal exposure to antidepressant medication and autism spectrum disorders in the offspring. The results of a cohort study[71] indicated that there is no increase in risk of ASD in the offspring of women who use selective serotonin reuptake inhibitors before pregnancy. A study[72] (n=942) was identified which aimed to examine the link between maternal hormonal treatments and ASD. Analysis of the results suggested that maternal hormonal interventions were associated with an increased risk of ASD.		

3 studies considered the risk of ASD following fertility treatment. A case-control study[73], including 4,164 autistic cases and 16,582 matched controls, indicated that there is no increase in risk of ASDs in children born after IVF. However, the results of a prospective cohort study[74] suggested that there was an increased risk of ASD in children born after ovulation induction with or without insemination compared to spontaneously conceived children. Another prospective cohort study[75] found that overall IVF treatment was not associated with autistic disorder but that there was a small increased risk associated with IVF using intracytoplasmic sperm injection for male infertility. A study[76] was identified which found that severe maternal hypothyroxinaemia at 6-18 weeks gestational age led to an increased likelihood of offspring developing autistic symptoms. <u>Environmental factors</u> A cohort study[77] investigating the link between long-term exposure to air pollution and ASD in Taiwan was identified. A cohort of 49,073 children age less than 3 years was included in the study. The results indicated that the risk of newly diagnostic ASD increased according to increasing ozone, carbon monoxide, nitrogen dioxide, and sulphur dioxide levels.		
Clinical area: Following referral		
Q: 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		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update</u> No evidence identified.	None identified.	The new evidence is consistent with the current evidence in the guideline which identifies

4 year surveillance review (2014) An observational study[78] (n=47) 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.		Neurofibromatosis as a factor associated with an increased prevalence of autism. The new evidence is unlikely to change the current guideline recommendation which states that information on factors associated with an increased prevalence of autism, including Neurofibromatosis, should be included in the referral letter to the autism team.
Clinical area: Following referral		
Q: 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?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update A prospective cohort study[79] was identified which assessed the level of symptoms of autism in children under 12 years who had been arrested for a first offence (n=308) compared with children from the general population. The findings of the study suggested that children who have been arrested 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 review (2014)** No evidence identified.	None identified.	The new evidence is 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.
Clinical area: Diagnostic assessment		
Q: What should be the components of the diagnostic assessment? When should they be undertaken, in what subgroups and in what order?: • 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)		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update Q-CHAT and AQ One study[80] aimed to determine whether 10 items	None identified.	A number of assessment tools specific to autism were identified in the new evidence. However, only some of the tools met the GDG's pre-defined

from the Autism Spectrum Quotient (AQ) and the Quantitative Checklist for Autism in Toddlers (Q-CHAT) showed equivalent sensitivity and specificity to the full versions. Results showed that all scores for the 10-item tools showed significant differences between the autism group and the control group and that each tool correlated significantly with its respective full version. Sensitivities for each tool ranged from 0.91 to 0.95 and specificities from 0.89 to 0.97. <u>ADI-R</u> A cohort study[81] assessed the potential impact of 'telescoping' (perceiving distant events as more recent than they are) on reports of the age of developmental milestones provided by caregivers of children with ASD. Through the ADI-R, carers were asked to estimate the age at which symptoms first manifested. The age of first reported concern did not differ significantly between time points for either the autism group or the control group, however, the reported age of first word increased over time for both groups suggesting that ADI-R scores may be affected by telescoping effects of parents' memories. A cohort study[82] investigated the development of new algorithms for scoring the ADI-R in children younger than 4 years (n=695). Analyses showed that items appearing in both the standard and toddler versions of the ADI-R were consistently more informative than items in only 1 version. Further analysis restricted to items appearing in both versions showed increased sensitivity and specificity compared to existing clinical cut-off algorithms: sensitivity of 85% and specificity of 70% for detecting autism versus non-spectrum disorders in the non-verbal group; for the single-word group the sensitivity was 94% and specificity		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 evidence is 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 is unlikely to impact on current guideline recommendations.

was 81%; and in the phrase-speech group the sensitivity was 80% and specificity was 70%. ADOS A cohort study[83] investigated the sensitivity and specificity of ADOS when used as an initial diagnostic assessment in children with suspected developmental delay or autism (n=584). The results showed that for detection of autism versus non-spectrum disorders, the sensitivity was 67–91% for communication and social domain scores and 82–94% for social affective and repetitive restricted behaviour domain scores. Specificity was 65–95% and 55–81% respectively. For detection of autism spectrum disorders other than autism versus non-spectrum disorders the sensitivity was 75–94% for communication and social domain scores and 72–100% for social affective and repetitive restricted behaviour domain scores. Specificity was 29–81% and 29–60% respectively. ADI-R and ADOS One study[84] investigated the combined use of the ADI-R and ADOS in children under the age of 4 years (n=595). Autism spectrum disorder was diagnosed in 435 children, 113 had non-spectrum disorders and 47 children had typical development. The results indicated that using the ADI-R clinical cut-off score and the ADOS together across all the groups had sensitivity of 90–98% and specificity of 80–92%. An observational study[85] reported on the clinical diagnosis of autism spectrum disorders in children and young people aged 4–18 years (n=2102). Children were assessed with the ADOS, and their parents were interviewed with the ADI-R and the Vineland Adaptive Behaviour Scales, and		

completed the Aberrant Behaviour Checklist. The results indicated that the strongest predictor of a diagnosis of autism was ADOS-measured social communication: 61% of children had moderate-to-severe social communication problems, and they were mainly diagnosed with autism. The remaining 39% of children with milder social communication problems included most of the children with a diagnosis of PDD-NOS or Asperger's disorder and about a third were diagnosed with autism. **4 year surveillance review (2014)** ASD-OC A study[86] examined the reliability of the autism spectrum disorder observation for children (ASD-OC) in 114 children. The results indicated that the measure had high internal consistency and reliability. ADI-R A study[87] assessing the Japanese version of the Autism Diagnostic Interview-Revised (ADI-R-JV) found that the tool had a sensitivity and specificity for correctly diagnosing autistic disorder of 0.92 and 0.89, respectively. However, sensitivity for individuals younger than 5 years was much lower at 0.55. A study[88] was identified which aimed to identify items from the ADI-R which would enable early identification of children with Asperger syndrome (AS). A clinical sample of 43 children with ADHD and 62 children with AS was used. Analysis of the ADI-R identified 8 items which would act as good predictors for AS. The results showed that the 8-item interview had high sensitivity (0.92) and specificity (0.90) for identifying children with AS up to 11 years old.		

ADOS A study[89] was identified which indicated that 8 items from the 29 in the Autism Diagnostic Observation Schedule-Generic (ADOS) were able to classify autism with 100% accuracy in 612 people with autism and 15 non-spectrum individuals. Further validation found that the 8 items had almost 100% sensitivity and 94% specificity suggesting its utility as an effective tool for identifying autism. ADOS/ADI-R A study[90] examining the diagnostic validity of the Autism Diagnostic Interview-Revised (ADI-R) and the revised Autism Diagnostic Observation Schedule (ADOS) was identified. 268 children (171 with ASD) were included in the study. Used together, the tools achieved a sensitivity of 77%-80% and specificity of 87%-90%. However, individually, the ADOS provided a better diagnostic accuracy than the ADI-R. CASS The results of a study[91] examining the Coolidge Autistic Symptoms Survey (CASS) found that it was able to differentiate between a group of children with Asperger's Disorder, children without an autism diagnosis but who were considered loners by their parents, and typically developing children. 3Di A study[92] examining the effectiveness of a translated version of the short version of the Developmental, Dimensional and Diagnostic Interview (3Di) was identified. Two groups of Thai children, including 63 with ASDs and 67 typically developing children, were interviewed with the short 3Di translated version. Sensitivities ranged		

from 66.7% to 85.7% across the domains of the tool, and specificities from 73.5% to 80.9%. CARS2 A study[93] assessing the reliability of the Lebanese version of the Childhood Autism Rating Scale Second Edition, High Functioning Version (CARS2-HF) found that the test had a high degree of internal consistency and reliability for identifying individuals with autism spectrum. A study[94] validating the Childhood Autism Rating Scale-Second Edition-Standard Version (CARS2-ST) for the Lebanese population found that the tool had good reliability and internal consistency when assessing for ASD in children.		
Clinical area: Diagnostic assessment		
Q: What should be the components of the diagnostic assessment? • Biomedical investigations for diagnosis of autism, for example electroencephalography (EEG), brain scan, genetic tests, counselling; investigations for associated medical conditions.		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update EEG A study[95] of EEG coherence (a measure of the connectivity between different parts of the brain) in children with autism (n=430) compared with neurotypical children (n=554) was identified. The results indicated that 40 coherence factors were found to account for 51% of variation between the autism and control groups. Genetic tests A cohort study[96] was identified to examine the diagnostic yield of genetic testing in children and young people with ASD. Genetic tests were carried out in 207 children. The diagnostic yield of	None identified.	There is considerable variation across the new evidence for biomedical investigations for diagnosis of autism with few of the studies reporting a confirmed diagnosis of autism as a result of the test undertaken. The evidence is 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.

the genetic testing was low with just 6% of cases found to have a genetic disorder. However, differences were observed between dysmorphic features, with 80% of tests normal, compared to 97% if no dysmorphic features were present. **<u>4 year surveillance review (2014)</u>** <u>Other</u> A study[97] was identified which examined scalp hair concentrations of trace elements in 1,967 autistic children. Analysis of the results showed that 29.7% were deficient in zinc and 17.6% in magnesium. 17.2% also suffered from high burdens of aluminium. <u>Neuroimaging</u> A systematic review and meta-analysis[98] of diffusion tensor imaging studies in people with autism spectrum disorder was identified. The results suggest that there are significant differences in the superior longitudinal fasciculus, uncinate fasciculus, and corpus callosum in people with ASD compared to typically developing individuals. A study[99] was identified which used magnetic resonance spectroscopy to examine abnormalities in the pregenual anterior cingulate cortex (pACC) in children with ASD. The results of the study indicated hyperglutamatergia and other neurometabolic abnormalities in pACC in ASD compared to controls. A study[100] assessed the use of transcranial ultrasonography (TUS) via the temporal bone as a potential investigation for the presence of cortical abnormalities and increased extra-axial fluid in children with autism. 23 children with autism spectrum disorders and 15 neurotypical siblings		

were included in the study. 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. A study[101] was identified which aimed to evaluate positron emission tomography (PET) findings in patients diagnosed with infantile spasms and autism. A group of 24 patients with infantile spasms (15 with autism and 9 without) underwent PET examination. The results of the PET revealed that 87% of those 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. A study[102] was identified which investigated GABA concentrations in the brains of children with ASD using magnetic resonance spectroscopy and spectral editing methods. Creatine-normalized GABA+ ratios were measured in a group of 17 children with ASD and 17 typically developing children. The results indicated that there were reduced levels of Creatine-normalized 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. One case-control study[103] was identified which aimed to examine whether specific brain networks can differentiate between children with ASD and typically developing (TD) children. The results showed that maps of salience network hyperconnectivity discriminated children with ASD from TD children with 75% sensitivity and 80% specificity.		

<u>Blood and urine tests</u> A study[104] was identified which measured the serum levels of the desert hedgehog (Dhh) protein in 57 patients with autism and 37 age-matched healthy children. Analysis of the results indicated that the mean serum level of Dhh in patients with autism was lower than the level of normal controls but that there was no link serum level and age, gender or autistic severity. A study[105] was identified which measured the serum levels of macrophage-derived chemokine (MDC) and thymus and activation-regulated chemokine (TARC) in 56 autistic children and 32 healthy matched children. The results indicated that children with autism had higher serum levels of MDC and TARC, and that increased levels were particularly associated with severe autism compared to mild to moderate autism. A study[106] was identified which measured the serum levels of IL-17A, a pro-inflammatory cytokine, in 45 children with autism and 40 matched healthy children. The results indicated that children with autism had higher serum levels of IL-17A levels with increased serum levels found in 48.9% of the autism group. Levels of IL-17A were correlated with severity of autism. A study[107] was identified which aimed to assess if blood tests reflecting humoral immunity are useful in identifying children with regressive autism. 24 children with a new diagnosis of regressive autism and 24 healthy children were included in the study. Analysis of the results found that the humoral immunity profile had a sensitivity of 79% and a specificity of 83% for identifying children with autism.		

A study[108] examining potential blood-based ASD biomarkers in 60 infants and toddlers at risk for ASDs, 34 at-risk for language delay, 17 at-risk for global developmental delay, and 68 typically developing children was identified. The mRNA expression profile in peripheral blood mononuclear cells was measured in each child. 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. A study[109] investigated the serum 25-hydroxyvitamin D (25(OH) D) levels in Chinese children with ASD. The results suggest that children with ASD had lower mean serum 25(OH) D levels compared to controls and that there is a link between serum and autism severity. A study[110] investigating the antioxidant specificities in plasma and red blood cell haemolysate from 25 infantile autistic children found that there were differences in some of the antioxidant enzyme levels in children with autism. A study[111] was identified which found that children with autism had higher corticosteroids excretion levels compared to controls and those with low and medium autism severity had high level of corticosteroids in the urine. A study[112] was identified which aimed to evaluate pentacarboxyl and coproporphyrins as urinary biological markers of ASD in 76 male children, including 30 with autism, 14 with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), and 32 neurotypical controls. The results showed that 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. A study[113], including 69 individuals with ASDs, was identified which aimed to determine if amino or organic acid biomarkers could be used to identify individuals with ASDs. The results indicated 87% of the group had increased levels of urine aspartic acid, 69% had increased levels of plasma taurine, and 72% had reduced plasma cysteine. <u>Genetic tests</u> One study[114] (n=65) was identified which conducted FMR1 gene analysis to confirm the diagnosis of fragile X syndrome in ASD cases in Indonesia. Analysis of the results showed that the fragile X site and FMR1 full mutation allele were identified in 4.6% and 6.15% of participants respectively. A study[115] was identified which used a custom-designed oligonucleotide array comparative genomic hybridization to identify copy-number variants (CNVs) which contribute to ASDs. From a cohort of 145 participants with ASDs, 16 CNVs were identified in 12 participants of which 5.5% were considered likely to contribute to ASDs. In a study[116] of 615 participants with ASD, analysis was carried out using both single-nucleotide polymorphism (SNP) and comparative genomic hybridization (CGH) arrays to identify copy number variations (CNVs) to highlight potential risk genes for ASD. The results indicated that the 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. A study[117] was identified comparing high-resolution comparative genomic methods for hybridization (HRCGH) and molecular karyotyping (array CGH) for identifying genomic abnormalities in children with mental retardation and autism. Using HRCGH, genomic rearrangements were identified in 46% of cases. CGH array identified different genomic abnormalities and genomic variations in 88% of cases and unbalanced genomic rearrangements in 52% of cases. A study[118] was identified which used chromosomal microarray analysis to identify copy number variants (CNVs) in 215 patients with autism or autism spectrum disorders (ASD) or developmental delay/learning disability. Analysis of the results indicated that 21% of participants had abnormal microarray results. One study[119] was identified which aimed to demonstrate the usefulness of Chromosomal microarray (CMA) as a clinical diagnostic test for individuals with developmental delay, intellectual disability, and autism spectrum disorders. 349 children and young people were included in the study. 91 CNVs were detected in 22% of participants of which 23% had intellectual disability and ASDs. A case-control study[120] was identified which analysed the frequency of the MTHFR gene C677T polymorphism using a polymerase chain reaction-restriction fragment length polymorphism assay in 186 children with autism and 186 controls. 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[121] was identified which used polymerase chain reaction-restriction fragment length polymorphism to assess the impact of the catechol-O-methyltransferase (COMT) gene Val158Met polymorphism on ASD risk in Chinese children. Analysis of the results indicated that the frequency of the Val158 genotype in children with ASD was lower than in healthy controls. One study[122] 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[123] identified a number of genetic variants within the metabotropic glutamate receptor 7 (GRM7) gene associated with ASD. One study[124] was identified which used whole-genome sequencing (WGS) to detect de novo or rare inherited genetic variants likely to be associated with ASD. 32 families with ASD were included in the study. Deleterious de novo mutations were found in 19% of families and X-linked or autosomal inherited alterations in 31% of families. One study[125] reported an association between two genetic markers (rs4307059 T allele and rs35678 TC genotype) and ASDs. The AFF2 genomic region was sequenced in 202		

males with ASD. The results indicated that compared to controls, there was a significant enrichment in participants with ASD[126]. The results of meta-analysis[127] 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. One study[128] 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.		
Clinical area: Diagnostic assessment		
Q. What is the stability of an autism diagnosis over time?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update Two studies were found relating to the stability of a diagnosis of autism over time. A cohort study[129] 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. Secondly, a systematic review[130] examined the stability of an autism diagnosis. The review, including 23 studies (n=1363), 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	Two GDG members highlighted that new the diagnostic criteria for ASD – DSM-5 – were published in 2013. One of the GDG members also stated that there have been some studies published which have examined differences between DSM-IV and ICD-10 which might highlight considerations relevant to the application of DSM-5. However, no references were provided.	The new evidence relates to both the stability of a diagnosis over time as well as the stability of the diagnosis based on DSM and ICD-10 criteria. The evidence relating to stability of the diagnosis over time suggests that children may show different symptoms of autism that could change their diagnosis. This supports the current recommendation which states that a child or young person should remain under review if there is uncertainty about the diagnosis. The new evidence relating to the new DSM-5 criteria for ASD suggests that DSM-5 may under-diagnose ASDs compared to the previous DSM-IV criteria. However, the DSM-5 criteria were only published in 2013, therefore it may be premature at this time to support an update in this area.

of children that had moved from a diagnosis of autism to another autism spectrum disorder or moved off the spectrum completely. Two studies were included relating to DSM-IV and DSM-5 as diagnostic criteria for ASD. One study[131] investigated DSM-IV-TR criteria in children (n=89) with intellectual disabilities. The sensitivity of DSM-IV-TR criteria for diagnosing autism ranged from 33% to 74% and specificity ranged from 45% to 88%. Another study[132] investigating the use of proposed DSM-5 criteria for classifying autism symptoms reported that 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. **4 year surveillance review (2014)** Five studies were identified relating to the new DSM-5 as diagnostic criteria for ASD. One Study[133] investigating the implications of the proposed DSM-5 criteria for ASDs was identified. Of the 210 participants included in the study who met DSM-IV criteria for a pervasive developmental disorder (PDDs), only 57.1 % met DSM-5 criteria. Another study[134] explored the proposed DSM-5 criteria for ASD in a group of 131 children previously diagnosed with either Autistic Disorder or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS). The results found that 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. One study[135] assessing the potential impact of the		Furthermore, the guideline recommends that health care professionals should consider referring children and young people with 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 to appropriate services. It is therefore unlikely that the new evidence will impact on the current guideline recommendations.

DSM-5 ASD criteria on ASD prevalence reported that out of 6577 children classified as having ASD based on the DSM-IV criteria, 81.2% of the group met the new DSM-5 criteria. One study[136] (n=424) which examined the differences between DSM-5 and DSM-IV-TR found that 36% of participants with ASD would no longer meet the criteria under the proposed DSM-5. A study[137] was identified which evaluated the proposed DSM-5 criteria for ASD in children with DSM-IV diagnoses of pervasive developmental disorders. 4,453 children with DSM-IV clinical PDD diagnoses and 690 with non-PDD diagnoses were included in the study. Based on parent data, the proposed DSM-5 criteria identified 91% of children with clinical DSM-IV PDD diagnoses. DSM-5 had a specificity of 0.53 overall which increased to 0.63 based on data from both parent and clinical observation.		
Clinical area: Diagnostic assessment		
Q. What is the agreement of an autism diagnosis across different diagnostic tools?		
Evidence summary	**GDG/clinical perspective**	**Impact**
Evidence Update No evidence identified. **4 year surveillance review (2014)** A study[138] was identified which aimed to assess the agreement between the DSM-5 ASD criteria and the Childhood Autism Rating Scale (CARS) and Checklist for Autism Spectrum Disorder (CASD). 143 children with ASD and other disorders were included in the study. There was high diagnostic agreement (94%) between the CARS and CASD but agreement between the CARS and CASD and DSM-5 was lower at 84%	None identified.	The new evidence relates to agreement between different diagnostic tools and the new ASD diagnostic criteria, DSM-5. There is variable evidence showing agreement across the different tools. In the original guideline the GDG 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 is unlikely that there will be sufficient evidence to make any recommendations in this area.

and 88% respectively. Another study[139] assessed agreement between DSM-5, DSM-IV, and the Checklist for Autism Spectrum Disorder in 125 children with ASD. Sensitivities for low and high functioning autism were high 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 an ASD. A study[140] examining the impact of DSM-5 on the diagnostic status of 498 participants with high-functioning ASD was identified. Satisfaction of DSM-5 requirements was dependent on the methodology used to document DSM-5 symptoms. Using data from the Autism Diagnostic Observation Schedule (ADOS) only 33% of participant 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.		
Clinical area: Assessment of co-existing conditions		
Q: Which are the common coexisting conditions that should be considered as part of assessment? • Neurodevelopmental: speech and language problems, intellectual disability, coordination, learning difficulties in numeracy and literacy		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update</u> No evidence identified. **<u>4 year surveillance review (2014)</u>** A study[141] was identified which aimed to describe the developmental characteristics of 129 children referred for clinical assessment due to suspicion of autism spectrum disorder. 100 of the 129 children met the criteria for ASD, of which 36% had and intellectual developmental disorder, 56% had	None identified.	The evidence relating to co-existing neurodevelopmental conditions, including intellectual disability and language disorder, is consistent with the conditions identified in the guideline.

language disorder, 37% had hyperactivity, and 7% had epilepsy. A study[142] was identified describing the characteristics of autistic regression in children with ASD compared to children with ASD and no reported regression. 35 children with ASD and reported developmental regression and 35 children with ASD and no reported regression were included in the study. The results indicated that regression of language, social skills and cognition were important characteristics of the regression-autistic group.		
Clinical area: Assessment of co-existing conditions		
Q: Which are the common coexisting conditions that should be considered as part of assessment? • Mental and behavioural disorders, such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety, depression, Tourette, tic disorders		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update</u> No evidence identified. **<u>4 year surveillance review (2014)</u>** A study[143] was identified which utilised DSM-IV-referenced rating scales to identify the most common psychiatric impairing conditions in children (n=115) with autism spectrum disorders. The results found that the most common conditions were attention-deficit/hyperactivity disorder, oppositional defiant disorder and anxiety disorder. A study[144] of the clinical characteristics of 108 high functioning young people with an autism spectrum disorder and anxiety found that the most common anxiety disorders in the group were social phobia and generalized anxiety disorder. 92% of participants also had two or more types of anxiety	None identified.	The evidence relating to co-existing mental and behavioural conditions, including ADHD and anxiety disorders is consistent with the conditions identified in the guideline.

disorder. A study[145] 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.		
Clinical area: Assessment of co-existing conditions		
Q: Which are the common coexisting conditions that should be considered as part of assessment? • Medical or neurological problems such as functional gastrointestinal problems, tuberous sclerosis, neurofibromatosis		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update</u> No evidence identified. **<u>4 year surveillance review (2014)</u>** A study[146] of 170 Chinese autistic children found an association between autistic regression and febrile seizures and a family history of neuropsychiatric disorders. One study[147] including 663 participants, aged 18 months to 15 years, diagnosed with ASD reported that prevalence of autistic regression and minor neurological and musculoskeletal deficits were higher in females than males. Two studies were identified which suggested an association between iron deficiency and ASD. One retrospective study[148] reported that iron deficiency in children with ASD may be more common than in the general population although no comparative figures were reported in the abstract. Further analysis proposed problems sucking, swallowing or chewing; poor eating behaviour; and inadequate amounts of meat, chicken, eggs or fish were risk factors for deficiency in this group. A second study[149] assessing the link between psychiatric disorders	None identified.	The new evidence is unlikely to impact on current guideline recommendations. The majority of studies identified through the literature search relate to conditions described in the current guidance. However, two studies indicated that there is a link between iron deficiency and ASD, although one of the studies suggested that this was the result of poor eating behaviour and inadequate protein intake. Feeding problems, including restricted diets, is one of the conditions listed in the guideline for consideration as part of an assessment. The results of another study indicated that there is an increased risk of ASD in people with Klinefelter syndrome. The guideline recommends that genetic abnormalities should be considered as part of an assessment, and therefore as a genetic disorder, it is unlikely that the evidence on Klinefelter syndrome would be sufficient to impact on the recommendations.

and iron deficiency anaemia among children and adolescents found that IDA increased the risk of psychiatric disorders, including autism spectrum disorder. One study[150] assessing symptoms associated with ASD in children with neurological disorders found 14.1% prevalence of ASD in a group of 99 children with a neurological disorder. The results of four studies reported varying prevalence rates of epilepsy in ASD. One study[151] found that in a group of 121 autistic children, 33.3% had epilepsy. A retrospective study[152] of 4,180 people with Asperger's syndrome found that 3.9% were registered with at least one epilepsy diagnosis compared to a general population estimate of 2%. Another study[153] reported that the average prevalence of epilepsy in children aged 2-17 years with ASD was 12.5%. One study[154] reported that in 65 children with epilepsy, 37% were screened positive for autism. A study[155] assessing comorbid disorders in 89 children and adolescents with Autism Spectrum Disorder found that 46% of participants had a comorbid disorder, in particular, epilepsy (10.1%), ADHD (18%) and an anxiety disorder (15.7%). One study[156] examining the co-occurrence of autism spectrum disorder (ASD) with vision impairment and hearing loss was identified. The results indicated that around 6-7% of children with vision impairment or hearing loss had co-occurring ASD. Another study[157] of 407 children with autism or a related disorder found that 40% of participants had an ophthalmic abnormality, including significant refractive errors (29%), strabismus (21%) and amblyopia (10%). A study[158] was also		

identified which highlighted ocular abnormalities in children diagnosed with an ASD. 44 children were included in the study, of which 52% were found to have an ocular abnormality. The abstract reported that prevalence is higher than in the general population although no prevalence rates for the general population were reported. Five studies examined links between ASDs and gastrointestinal disorders. Of these, one study[159] (n=242) found that 29% of children presenting with functional defecation disorders at a specialised outpatient clinic had co-occurring ASD symptoms. Another study[160] comparing gastrointestinal problems in children with ASD, developmental delay (DD) and typical development found that frequent GI symptoms were more common in children with ASD or DD compared to typically developing children. A study[161] which examined the link between ASDs and coeliac disease found that individuals with a positive coeliac disease serologic test result had an increased risk for later diagnosis of an ASD. Another study[162] examining gastrointestinal dysfunction (GID) in ASD indicated that functional constipation was the most common type of GID in children with ASD (85.0%). However, one study[163] evaluating gut permeability in children with ASD compared to children with a special educational need found that there was no increased risk of small intestine permeability associated with autism spectrum disorders. A study[164] was identified which assessed the prevalence of cerebral palsy in a group of individuals with Asperger's syndrome (n=4180). The results of the study indicated that people with AS have an increased risk of cerebral palsy relative to the general population. Another		

study[165] examining the prevalence and characteristics of children with cerebral palsy reported that the frequency of co-occurring ASD was 6.9%, with 18.4% frequency in non-spastic cerebral palsy. A study[166] (n=1596) investigating the association between ASDs and allergic and autoimmune diseases found that participants with ASDs had an increased risk of asthma, allergic rhinitis, atopic dermatitis, urticaria, and type 1 diabetes. A sample of 860 Klinefelter patients was compared to 86,000 matched control in a study[167] aimed at assessing the risk of psychosis, autism and ADHD Klinefelter syndrome. Analysis of the results indicated that there is an increased risk of autism spectrum disorder in people with Klinefelter syndrome. One study[168] examined the health, physical and behavioural problems in a group of individuals diagnosed with ASD (n=54). A number of co-existing conditions were reported including eating disorders (94%), obsessive-compulsive behaviours (92%), behavioural problems (89%), and sensory processing problems (85%).		
Clinical area: Recognition (Research recommendation)		
Q: 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?		
Evidence summary	**GDG/clinical perspective**	**Impact**
<u>Evidence Update</u> No evidence identified. **<u>4 year surveillance review (2014)</u>** An observational study[169] was identified which aimed to assess the effectiveness of a training	None identified.	The new evidence is 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

programme on rates of diagnostic identification of autism spectrum disorder within a community paediatric setting. 27 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.		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.

For the following areas of the guideline no new evidence was identified:

- When a child or young person should be referred for diagnostic assessment
- Other assessment tools to assist interpretation of the autism-specific diagnostic tools
- Multidisciplinary assessment versus single practitioner assessment
- Differential diagnoses of autism
- Communicating the findings of diagnostic assessment to children and young people, and their families/carers
- Actions following assessment for children and young people who are not immediately diagnosed with autism
- Information and support
- Routine additional information from educational settings to improve accuracy in diagnosing autism
- Additional assessments to improve accuracy in diagnosing autism among preschool children
- The effectiveness and acceptability of comparative genomic hybridisation (CGH) array compared with current genetic testing in children and young people with identified autism.

Ongoing research

None identified.

Anti-discrimination and equalities considerations

None identified.

Conclusion

Through the 4 year surveillance review of CG128, no new evidence was identified which may potentially change the direction of current guideline recommendations. The proposal is not to update the guideline at this time. It is not recommended that this guideline be added to the

static guidance list as we are aware that DSM-5 is currently being implemented and are unsure on the potential impact that this may have on the guideline. As such, we will monitor this area at the next surveillance review of the guideline in 2 years' time.

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