NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Clinical Practice – Surveillance Programme

Recommendation for Guidance Executive (post consultation)

Clinical guideline
CG128: Autism diagnosis in children and young people

Publication date
September 2011

Surveillance report for GE (post consultation)
August 2014

Surveillance recommendation
GE is asked to consider the following proposal which was consulted on for two weeks:

- The clinical guideline CG128: Autism diagnosis in children and young people should not be considered for an update at this time.

Key findings

			Potential impact on guidance	
			Yes	**No**
Evidence identified from Evidence Update				✓
Evidence identified from literature search				✓
Feedback from Guideline Development Group				✓
Anti-discrimination and equalities considerations				✓
No update	CGUT update	Standard update	Transfer to static list	Change review cycle
✓				

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Centre for Clinical Practice – Surveillance Programme

Surveillance review of CG128: Autism diagnosis in children and young people

Recommendation for Guidance Executive

Background information

Guideline issue date: 2011
4 year review: 2014

NCC: Women's and Children's Health

Four year surveillance review

1. An Evidence Update was produced for this guideline in April 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.

2. For the 4 year Surveillance Review, a search to identify new evidence was carried out for studies 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 obtained from members of the guideline development group (GDG) through a questionnaire. Generally the GDG felt that the guideline does not need to be updated.

3. No new evidence was identified through the literature search which would invalidate the guideline recommendations.

Ongoing research

4. None identified.

Anti-discrimination and equalities considerations

5. Through stakeholder consultation, it was identified that females are being discriminated against in the assessment and diagnosis of autism. The guideline currently recommends that when considering the possibility of autism, health care professionals should be aware that autism may be under-diagnosed in girls. There is also a research recommendation in the guideline relating to training for professionals to recognise signs and symptoms of autism to lead to earlier assessment of needs and earlier diagnosis, particularly where it might benefit at-risk groups such as girls. One observational study was identified through the surveillance review which reported an increase in the identification of children with autism spectrum disorder following training. However, the abstract provided no information to suggest any comparisons were made with clinical services where the additional training was not available. Nor was there any information regarding effectiveness in terms of impact on under-diagnosed groups and earlier referral rates. As a result, this evidence was considered insufficient to answer the research recommendation.

Implications for other NICE programmes

6. A Quality Standard for Autism (covering autism in children, young people and adults) (QS51) was issued in January 2014.

7. A no to update decision is unlikely to impact on any of the Quality Statements within the Quality Standard.

Summary of stakeholder feedback

8. Stakeholders were consulted on the following proposal over a two week consultation period:

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

9. In total, nine stakeholders responded to the consultation. Only five stakeholders provided comments on the surveillance review proposal and the remaining four stakeholders stated that they had no substantive comments to make.

10. Of the five stakeholders that provided comments on the surveillance review proposal, four disagreed with the proposal to not update the guideline at this time and one stakeholder agreed.

11. Stakeholders highlighted a number of references as part of their consultation comments. Through an assessment of the abstracts, however, none of the studies were considered to impact on the guideline recommendations.

12. The following is a summary of the general comments made by the stakeholders that disagreed with the proposal not to update the guideline:

a) Signs and symptoms

One stakeholder felt that problems with under-diagnosis both in girls and in children with higher communication capabilities need to be addressed. The guideline already makes recommendations relating to both of these issues and no evidence was identified which would be likely to impact on these current recommendations.

b) Diagnostic assessment tools

The evidence in the guideline for diagnostic tools did not support the use of a single tool to arrive at a diagnosis and therefore it was recommended: do not rely on any autism-specific diagnostic tool alone to diagnose autism. There was also no consistent evidence identified in the surveillance review to recommend the use of one specific diagnostic tool. However, one stakeholder stated that diagnostic tools, such as ADOS-2, are relied upon by clinicians in making a diagnosis, despite the recommendation in the guideline. Another stakeholder highlighted new evidence relating to the revised Diagnostic and Statistical Manual of Mental Disorders (DSM-5) which was published in May 2013. It was stated that the guideline should be updated to reflect changes to the diagnostic criteria. The surveillance review acknowledged changes to the diagnostic criteria, however, it was considered that at this time there was insufficient evidence available relating to the potential impact of DSM-5 on the guideline. It is therefore proposed that the guideline remains on the active surveillance list and that the impact of DSM-5 is monitored at the next surveillance review.

c) Medical investigations

One stakeholder felt that clinicians are unaware of the current guideline recommendation to consider genetic tests and electroencephalography in individual circumstances and based on physical examination, clinical judgment and the child or young person's profile, although no evidence was provided to support this statement. Another stakeholder highlighted a number of studies relating to various antibodies, metabolic biomarkers and chemical changes in the brain and potential links to autism or autism spectrum disorders (ASD). The studies were relatively small trials and none provided evidence of a medical test which confirmed a diagnosis of autism or ASD. It was considered that additional evidence would be needed before these areas could be considered for inclusion in the guideline and these areas will be monitored in future surveillance reviews of the guideline.

d) Stability of the diagnosis

One stakeholder stated that autism varies according to an individual's environment and that a supportive environment can hide autistic traits. This was an issue that was highlighted in the guideline and a recommendation was made which states: consider the possibility of autism when older children or young people present for the first time with possible autism, as signs or symptoms may have previously been masked by the child or young person's coping mechanisms and/or a supportive environment. Another stakeholder disagreed that autism is a lifelong condition and provided references regarding individuals who had lost their diagnosis of autism. In an assessment of the abstracts, the studies indicated that reduced symptoms or a loss of autism diagnosis were the result of early interventions. However, both treatment and reassessment and review of diagnosis are out of scope of this guideline.

e) Co-existing conditions

One stakeholder stated that co-existing conditions are not considered by clinicians as standard but provided no evidence to support this statement. Another stakeholder highlighted a number of references relating to co-existing conditions which they felt were not adequately covered in the current guideline. These included allergic manifestations, gastrointestinal problems and mitochondrial dysfunction. In summary, many of the references provided were excluded from the present surveillance review due to the lack of data within abstracts to support study findings or because the studies were published prior to the search cut-off date for the present surveillance review (where relevant, these studies would have been identified through the development of the guideline or in the literature search for the Evidence Update). A number of references supported existing recommendations in the guideline, particularly relating to gastrointestinal problems. There were also a number of studies identified for co-existing conditions which would need additional consistent new evidence to support their findings before they can be considered for inclusion in the guideline. As such, these areas will be monitored in future surveillance reviews of the guideline.

f) Risk factors

One stakeholder provided references relating to risk factors for autism. One study was highlighted relating to the heritability of autism, however, this was consistent with existing evidence in the guideline. Another small study was highlighted which indicated that there was an increased risk of autism spectrum disorders in the children of mothers with antiphospholipid syndrome. Due to the size of the trial it was considered that further evidence would be needed before this risk factor could be considered for inclusion in the guideline.

g) Regression

One stakeholder highlighted a few studies relating to autistic regression following autoimmune and infectious encephalitis. This specific area is not currently covered in the guideline, however, the guideline does recommend that children and young people older than 3 years with regression in language, or children of any age with regression in motor skills, should be referred first to a paediatrician or paediatric neurologist. The studies identified by the stakeholder were case reports, therefore it was considered that further large-scale studies would be needed before this area could be considered for inclusion in the guideline.

h) Post-diagnosis

One stakeholder stated that the guideline should acknowledge that diagnosis is only the first step on the pathway. The stakeholder was referred to CG170: the management and support of children and young people on the autism spectrum and also to the NICE Pathway for Autism which describes the full range of care for children and young people with autism.

Conclusion

13. Through the 4 year surveillance review of CG128 and subsequent consultation with stakeholders, no new evidence was identified which may potentially change the direction of guideline recommendations. The proposal is not to update the guideline at this time.

14. It is not recommended that this guideline be added to the static guidance list. DSM-5 is currently being implemented and the potential impact that this may have on the guideline is currently unclear. Furthermore, there are a number of areas highlighted by stakeholders, particularly relating to evidence for potential co-existing conditions of autism, which will need to be monitored at the next surveillance review of the guideline.

Surveillance recommendation

15. GE are asked to consider the following proposal which was consulted on for two weeks:

- The clinical guideline CG128: Autism diagnosis in children and young people should not be considered for an update at this time.

Mark Baker – Centre Director
Sarah Willett – Associate Director
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Centre for Clinical Practice
August 2014

Appendix 1 Surveillance review consultation comments table - 30 June-11 July 2014

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Treating Autism	Disagree		Comments on proposal not to update the guideline We believe the guideline is both factually incorrect and incomplete and should be amended in several places. 1.1 Introduction: “Autism is a lifelong disorder” -- This statement in the guideline is incorrect, and should be amended to reflect recent studies, which found that a percentage of children on the autism spectrum present with decreasing symptoms, or even complete recovery from ASD (see below). “Autism is strongly associated with a number of coexisting conditions …” – The Guideline fails to mention many medical/physical conditions that are much more prevalent in autism than normal population or in other developmental disorders, and that the severity of those medical conditions are frequently found to be associated with severity of autistic impairments (see below). Page 16: 55 “Be aware that in children and young people with communication difficulties it may be difficult to recognise functional problems or mental health problems.” -- The Guideline fails to add here the difficulty in recognising pathological physical /medical problems, which is a great contributor to barriers to access to appropriate health care for individuals with autism (see below). Page 23: Table 4 Factors associated with an	Thank you for your comments and for highlighting references for this consultation. The references which met our inclusion criteria for the surveillance review were assessed and responses are given below. **Stability of the diagnosis** The studies by Fein et al., 2013 and Anderson et al., 2013 were identified through the literature search but were excluded from the surveillance review. In terms of the study by Fein et al., the abstract reported that individuals who had lost their diagnosis of autism had comparable scores with typically developing individuals across socialisation, communication, face recognition, and most language subscales. This study was excluded from the surveillance review because the abstract reported no data to support the study findings. The study by Anderson et al. reported that intellectual disabilities at age 19 were predicted by age 2 about 85% of the time using the scores from diagnostic and psychometric instruments. This study was considered to be beyond the scope of the guideline which was concerned with the recognition, referral and diagnosis of children and young people with autism and specifically excluded reassessment and review of diagnosis. The studies by Mukaddes et al., 2014 and Orinstein et al., 2014 were not identified through the literature search because they were published after the search cut-off date for the surveillance review. Mukaddes et al., 2014

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			increased prevalence of autism – The Guideline fails to include findings from three large recently published studies, which found increased prevalence of autism in areas with higher levels of pollution and use of pesticides. The Guideline also fails to mention increased prevalence of autism in mothers with various autoimmune conditions (see below). Page 33: "There is a substantial genetic basis with strong heritability" -- This statement is incorrect. The wording of the Guideline needs to be amended to include findings by Hallmayer (2011) and Sandin (2014), the two largest twin studied performed to date, which both found a substantial environmental risk component to autism. The genetic risk is much lower than estimated by previous twin studies, which are quoted in the Guideline but are much lower in quality and should be replaced with these newer, stronger findings. "Autism is strongly associated with a number of coexisting conditions" -- The Guideline fails to list physical/medical conditions that are very prevalent in autism (see below). 2.1.2 Onset and course of autism: -- The Guideline should be amended to include findings of regression into autism following autoimmune and infectious encephalitis, see below. Page 82: 4.7 Evidence statements: risk factors -- The Guideline fails to list autoimmune conditions in the family/mothers as an important risk factor (see below). Page 144: 7 Assessment of coexisting conditions -- Many relevant studies have been left out (see	reported a descriptive study about the characteristics of children (n=39) who had lost their diagnosis of autism. The abstract concluded that children with an autism diagnosis could lose the diagnosis if involved in an early intervention. The results of the study by Orinstein et al., 2014 reported in the abstract indicated that children with ASDs who no longer meet diagnostic criteria for any ASD and reach normal cognitive function (optimal outcomes) had generally received earlier and more intensive interventions than children with high-functioning autism who received more pharmacologic treatments. The main findings from the studies by Mukaddes et al. and Orinstein et al. suggest that earlier interventions improve outcomes for people with ASDs. This is outside the scope of this guideline and relates to CG170 which covers the management and support of children and young people on the autism spectrum, including interventions, and covers the outcomes associated with core and non-core features of autism. **Co-existing conditions** Thank you for your comments and for highlighting references relating to autism and co-existing conditions. The Guideline Development Group (GDG) reviewed the evidence for a number of different conditions, however, to determine whether a condition should be considered a coexisting condition with autism, the GDG agreed that a condition should have at least one of the following characteristics: • a documented prevalence rate of the condition in children and young people

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			below). Page 153: Recommendations -Number Recommendation 54 “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…” – The Guideline fails to mention here other medical comorbidities frequently present in autism (see below). Page 176: Recommendations - Number Recommendation 59 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: Many common medical conditions are now known to be significantly more prevalent in people with ASD compared to the general population and other developmental conditions. Premature mortality is also significantly increased in ASD. The guideline fails to mention these medical conditions, with the exception of epilepsy. Recent large-scale studies have confirmed that individuals with ASD have much higher than expected rates of various medical conditions studied, including: food allergies, allergic rhinitis, atopic dermatitis, ear and respiratory infections, type I diabetes, asthma, gastrointestinal problems, sleep disorders, schizophrenia, headaches, migraines, seizures and muscular dystrophy (Chen, 2013; Gurney, 2006; Isaksen et al., 2012; Kohane et al., 2012; Mazurek et al., 2012; Schieve et al., 2012). A recent large-scale	with autism higher than that for the general population • likely to benefit from appropriate intervention(s) • likely to have an important impact on quality of life. The GDG also considered the ease of diagnosis, defined as diagnostic accuracy, and the cost effectiveness of treatment of the condition if identified. The studies by Isaksen et al., 2012 and Mazurek et al., 2012 were identified through the literature search for the surveillance review but were excluded because there was insufficient data presented in the abstracts to support the study findings. Isaksen et al. reported that a high number of specific medical conditions occurred more frequently in individuals with childhood autism than in the other diagnostic sub-groups but no data was presented in the abstract. Mazurek et al. reported that anxiety, sensory processing problems, and gastrointestinal problems are potentially related to ASD in children. This is consistent with the guideline which already considers these problems as signs & symptoms of autism and potential co-existing conditions. The study by Venkat et al., 2012 was identified through the literature search for the surveillance review but was excluded because an assessment of the abstract indicated that it was a commentary of existing evidence rather than a report of a study. Thank you for providing the reference for the Treating Autism Survey (2014). Unfortunately

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			study that examined health records of 2.5 million individuals found significantly higher than normal rates of nearly all major medical disorders in individuals ASD, including GI disorders, epilepsy, dyslipidemia, vision and hearing impairments, hypertensions, autoimmune conditions, asthma, allergies, osteoporosis and others, extending across all age groups (Croen et al., 2014). Secondly, while persons with ASD have higher rates of medical comorbidity and early mortality, they also consistently experience barriers in accessing appropriate medical care (Gurney, 2006; Liptak et al., 2006; Tregnago, 2012). Combined with the behavioural manifestations of ASD and difficulties with communication, these medical conditions generate challenges to clinicians regarding recognising, assessing, and managing the illness (Olivie, 2012; Venkat et al., 2012). In a 2014 survey conducted by Treating Autism of families with ASD (n=304) only 22% of respondents reported that "the person with ASD had a thorough investigation of his/her symptoms from an NHS practitioner". When asked what type of symptoms NHS professionals had dismissed as the result of ASD, answers included frequent vomiting, severe constipation, hyperactivity, diarrhoea, screaming, self-injury, sleeping only a few hours a night, seizure-like behaviours, aggressive outbursts, failure to grow, contorting/posturing, excessive drinking of water, toe-walking, chewing/eating non-food items, tics and jerks. (Treating Autism survey, 2014). In order to ensure that patients with ASD are not disenfranchised from the healthcare system it is of paramount importance that health	this type of information does not meet the criteria for evidence which would be included in the NICE surveillance process. The studies provided as examples of "diagnostic overshadowing" were not identified through the literature search because they were published prior to search cut-off date for the surveillance review (see full list below). Currently, the guideline recommends that a medical history, including past and current health conditions, and a physical examination should be included in every autism diagnostic assessment. Failure to follow this recommendation is an implementation issue. ***Autism and allergies*** A number of references were provided relating to allergic manifestations and links to ASD. The study by Chen et al., 2013 was identified through the literature search and was summarised in the consultation document for the surveillance review. The study by Croen et al., 2014 was not identified through the literature search for the surveillance review, however, as this study aims to describe the frequency of psychiatric and medical conditions in adults with ASD, it is out of scope of this guideline which covers children and young people only. The study by Shibata et al., 2013 was identified through the literature search for the surveillance review. The results reported in the abstract indicated that children with higher ASD scores on the Autism Screening Questionnaire had an increased prevalence of nasal allergy. However, the study was excluded from the surveillance review because no data was presented in the abstract to support these findings. Following an assessment of the abstracts, it is considered that further consistent

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			professionals do not dismiss unusual symptoms and presentation of medical illness as being behavioural or 'a part of autism'. Pain and physical problems in individuals with ASD—especially for approximately 40% of the population with severe communication difficulties or intellectual disability —frequently present in atypical ways and therefore are often erroneously dismissed as behavioural or mental health problems. Published case studies provide examples of such 'diagnostic overshadowing' and illustrate how easily those unusual manifestations can be overlooked due to lack of awareness on the part of healthcare providers (Goldson and Bauman, 2007; Jones et al., 2008; Lea et al., 2012; Smith et al., 2012). It can be argued that dismissal of atypical manifestation of pain and physical issues as 'autism behaviours' represents outright discrimination towards patients, wherein 'a person is treated less favourably than someone else and that the treatment is for a reason relating to the person's protected characteristic', i.e. disability (Equality Act 2010). "Care providers should be aware that problem behavior in patients with ASDs may be the primary or sole symptom of the underlying medical condition, including some gastrointestinal disorders." (Buie et al., 2010). The current guideline is inadequate in this regard, as it fails to draw health professionals' attention to these issues. Comments regarding specific areas of mentioned in the 'CG128 Autism in children and young people: surveillance review proposal'	evidence is needed before allergic manifestations can be considered for inclusion in the guideline. ***Autism and Gastrointestinal problems*** The consultee highlighted several references relating to gastrointestinal comorbidities and ASDs. The current guideline considered gastrointestinal problems as co-existing conditions of autism and ASD, and recommended that health care professionals should consider whether a child or young person may have constipation, altered bowel habit, faecal incontinence or encopresis as a coexisting condition, and if suspected carry out appropriate assessments and referrals. The study by Chaidez et al., 2013 was identified through the literature search and summarised in the consultation document for the surveillance review. The abstract for the study reported that frequent GI symptoms were more common in children with ASD compared to typically developing children. The studies by Mazefsky et al., 2013 and Peters et al., 2013 were identified through the literature search for the surveillance review but were excluded because there was no data presented in the abstracts to support the study findings. In terms of the study by Mazefsky et al., 2013, the abstract reported that majority of children with autism in the study also had at least one gastrointestinal symptom. The study by Peters et al., 2013 reported that rigid-compulsive behaviours in children aged 2-17 with ASD were associated with constipation and diarrhoea or underwear staining. The study by McElhanon et al., 2014 was not identified through the literature search because it was published after the search

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			Regarding: Clinical area: Diagnostic assessment Q. What is the stability of an autism diagnosis over time? Page 31: “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.” There is now sufficient evidence (see below) that shows that even IF there is no uncertainty about the diagnosis there is a possibility that the child can lose their symptoms of autism later on. In other words even if it is absolutely certain that a child DOES exhibit all symptoms and meets full criteria and correctly receives the diagnosis of autism, it is still possible that those symptoms change over time and the child recovers from autism and moves off the spectrum. Some children on the autism spectrum present with decreasing symptoms, or even complete recovery from ASD (Anderson et al., 2013; 2012; Fein et al., 2013; Mukaddes et al., 2014; Orinstein et al., 2014; Pellicano, 2012). The wording of the Guideline should be changed to reflect these findings. Regarding: 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	cut-off date for the surveillance review. The abstract reported that children with ASD experience greater prevalence of gastrointestinal symptoms compared with control children, as well as higher rates of diarrhoea, constipation and abdominal pain. These studies are consistent with current guideline recommendations. The study by de Magistris et al., 2013 was not identified through the literature search for the surveillance review. The abstract reported that the prevalence of certain antibodies to gliadin and milk proteins were higher in autistic children compared to controls, and that intestinal permeability was also increased in ASDs. Additional consistent evidence is needed before this area can be considered for inclusion in the guideline. The study by Ming et al., 2012 was identified in the literature search for the surveillance review but was excluded because there was insufficient data reported in the abstract to support the study findings. The abstract reported that abnormal amino acid metabolism, increased oxidative stress, and altered gut microbiomes were found in children with ASD. The study was a small study of 48 children with ASD and 53 age matched controls, and therefore additional consistent evidence would be needed before this could be considered for inclusion in the guideline. The study by Walker et al., 2013 study was identified in the literature search for the surveillance review. The abstract reported that children with ASD have a gastrointestinal mucosal molecular profile similar to that of known inflammatory bowel disease. However, the study

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			functional gastrointestinal problems… We disagree that the new evidence should not impact on the current guideline recommendations. The current guidelines are inadequate and should be amended to a) draw attention to increased prevalence of many medical comorbidities in autism and b) to raise the issue and so help reduce widespread 'diagnostic overshadowing' in autism, where behavioural manifestations of medical problems are frequently dismissed as 'just autism' or some preconceived facet of the diagnosis. The current guidelines lacks in this regard and should be updated to reflect both the increased prevalence of various medical conditions in ASD and to call for better awareness and recognition of atypical manifestations of medical problems in children with ASD. High prevalence of the following medical comorbidities in children with Autism should be listed the Guideline, alongside mental health and other comorbidities: 1. Various allergic manifestations, including asthma, nasal allergies, atopic diseases (IgE-mediated), and food intolerances are now known to be common in ASD and to extend across all age groups (Chen et al., 2013; Croen et al., 2014; Kohane et al., 2012; Schieve et al., 2012). Furthermore, there appears to be a positive association between the frequency and severity of allergic manifestations and severity of autism, where allergic diseases have been observed to be linked to both the core symptoms of autism—impaired social interaction and communication	was excluded from the surveillance review because the abstract did not report any data to support the study findings. The study by Persico et al., 2013 was identified through the literature search for the surveillance review but was excluded because an assessment of the abstract indicated that it was a commentary of existing evidence rather than a report of a study. The study by Adams at al., 2011 was not identified as it was published before the search cut-off date for the surveillance review. The results reported in the abstract reported a link between gastrointestinal symptoms and autism severity. The study by Gorrindo et al., 2012 was identified through the literature search and was summarised in the consultation document for the surveillance review. The study examined gastrointestinal dysfunction (GID) in ASD and the results presented in the abstract indicated that functional constipation was the most common type of GID in children with ASD. Both studies are consistent with the current guideline recommendations regarding gastrointestinal problems. The study by Furuta et al., 2012 was identified in the literature search for the surveillance review. The abstract reported on the development of a constipation algorithm to identify, evaluate, and manage constipation in children with ASDs. The study was excluded from the surveillance review because the abstract did not report any data to support study findings. The reference provided for Coury et al., 2012 could not be assessed because no abstract was available for this study.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			and repetitive and stereotyped patterns of behaviours—as well as behaviours such as anxiety, hyperactivity, and irritability, commonly attributed to 'being autistic' or to having 'mental health' problems (Mostafa et al., 2008; Shibata et al., 2013). Health professionals should be aware that when a child or adult with autism presents with 'autistic irritability' or increased aggressiveness, anxiety, inability to fall or stay asleep, inability to concentrate, hyperactivity and daytime fatigue, the possibility of allergic and non-IgE hypersensitive conditions should be considered. Health professionals should be made aware of these important clinical issues through updated guidelines. 2. The connection between autism and autoimmune disorders: a number of studies demonstrating a high prevalence of family history of autoimmune conditions compared to general population. Maternal conditions such as diabetes, rheumatoid arthritis, lupus, psoriasis, celiac disease, antiphospholipid syndrome and autoimmune thyroid disease are significantly associated with a greater risk of ASD in the offspring (Abisror et al., 2013; Atladóttir et al., 2009; Mostafa et al., 2014; Sweeten et al., 2003) and a recent large-scale study reported that autoimmune disorders are found 20%-30% more often in adult females with ASD than controls (Croen et al., 2014). Finally, an association between serum levels of various autoantibodies in ASD individuals and severity of their autistic symptoms has been repeatedly observed (Chen et al., 2013; Frye et al., 2012; Mostafa and Al-Ayadhi, 2012). Health professionals, especially immunologists, neurologists and others who receive referrals should be aware of the potential	A number of references were provided relating to bacterial flora in individuals with ASD. The study by De Angelis et al., 2013 was identified through the literature search for the surveillance review. The abstract reported that that the main bacterial phyla (Firmicutes, Bacteroidetes, Fusobacteria and Verrucomicrobia) significantly differed in the fecal microbiota of children with Pervasive Developmental Disorder Not Otherwise Specified and autism in comparison to healthy controls, with the highest microbial diversity found in children with autism. However, the study was excluded because the abstract presented no data to support the study findings. ***Mitochondrial dysfunction*** The study by Goh et al., 2014 examined mitochondrial dysfunction as a neurobiological subtype of autism spectrum disorder. This study was not identified through the literature search because it was published after the search cut-off date for the surveillance review. The study assessed brain lactate in 75 children and adults with ASD compared with 96 typically developing controls. The results reported in the abstract indicated that individuals with ASD had a higher rate of lactate doublets were present at a significantly higher rate in participants with ASD (13%) compared to controls and that the presence of lactate was associated with increasing age. Additional evidence is needed before this area can be considered for inclusion in the guideline. The study by Ghezzo et al., 2013 was identified through the literature search for the surveillance review but was excluded because no data was presented in the abstract to support the study findings of oxidative stress markers in children

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			pathological role autoantibodies may play in some patients with ASD, especially those with a family history of autoimmune disease or seizure disorder. Guidelines should be changed to reflect and draw attention to these important clinical issues. 3. Gastrointestinal comorbidities are significantly over-represented in ASD and can often be related to problem behaviours, sensory overresponsitivity, dysregulated sleep, rigid–compulsive behaviours, aggression, anxiety and irritability (Chaidez et al., 2013; Mazefski et al., 2013; Mazurek et al., 2012; Peters et al., 2013; Schurman et al., 2012). The largest ever meta-analysis published in April 2014 in the Pediatrics journal confirmed a strong link between GI disorders and autism (McElhanon et al., 2014), and the results from a large-scale population-based study conducted by the US CDC showed that children with ASD, in addition to having many other unmet health needs, experience many more gastrointestinal problems than children with other developmental delays, those with learning disability, or typical controls (Schieve et al., 2012). GI disorders are also significantly higher in adults with ASD than normal, as confirmed by the largest study of its kind that examined medical records of more than 2.5 million adults (Croen et al., 2014). The guideline should be changed to reflect the findings of both functional bowel problems as well as pathological findings being more prevalent in children with autism, including gastroesophageal reflux, digestive enzyme deficiency, bacterial dysbiosis, increased intestinal permeability, diarrhoea, constipation	with autism. The study by Gu et al., 2013 was identified through the literature search for the surveillance review. The abstract reported that the results of the study indicated that autism is associated with mitochondrial dysfunction in the brain. However, the study was excluded from the surveillance review because it did not report details of the study population. Furthermore, there were no details of the tests confirming a diagnosis of autism as a result of abnormal results. The study by Legido et al., 2013 was identified through the literature search for the surveillance review but was excluded because an assessment of the abstract indicated that it was a commentary of existing evidence rather than a report of a study. The study by Muratore et al., 2013 was identified through the literature search for the surveillance review. The study reported on the measurement of methionine synthase (MS) mRNA levels in postmortem human cortex from subjects across the lifespan. The results presented in the abstract indicated that MS mRNA levels were significantly lower in autistic subjects, especially at younger ages, however, the study was excluded from the surveillance review because the abstract reported no data to support the study findings. The study by Napoli et al., 2014 was not identified through the literature search because it was published after the search cut-off date for the surveillance review. The abstract reported that the oxidative phosphorylation capacity of granulocytes was lower in children with autism

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			(de Magistris et al., 2010; 2013; Horvath et al., 1999; Kushak et al., 2011; Ming et al., 2012; Persico and Napolioni, 2012; Wang et al., 2012; Williams et al., 2011; 2012). In children with ASD undergoing endoscopy, high rates of lymphoid nodular hyperplasia, esophagitis, gastritis, duodenitis, and colitis have been described, and preliminary evidence suggests that some features may be unique to gastrointestinal inflammation specific to autism (Horvath et al., 1999; Torrente et al., 2004; Walker et al., 2013). Metabolic/biochemical changes found in the urine of individuals with ASD further confirm the gut microbiota abnormalities revealed by stool and ileal tissue investigations (Ming et al., 2012; Yap et al., 2010). The strong correlation of gastrointestinal symptoms with severity of autism indicates that children more severely affected by autism are likely to have severe gastrointestinal symptoms (Adams et al., 2011; Gorrindo et al., 2012; Wang et al., 2011). Recent research has also confirmed that presence of gastrointestinal dysfunction in children with autism is not associated with distinct dietary habits or medication status, and parental reporting of any GI dysfunction in their children is highly concordant with later clinical diagnosis of that dysfunction (Gorrindo et al., 2012). A consensus paper published in the journal of the American Academy of Pediatrics recommends that health care providers should be alerted to the behavioural manifestations of gastrointestinal disorders in patients with ASD, “as those can be atypical and evident only as a change in behavior, thus presenting a significant challenge to both parents and health care providers.”	than in typically developing children, and that higher oxidative stress in the cells of children with autism was evidenced by higher rates of mitochondrial reactive oxygen species production, higher mitochondrial DNA copy number per cell, and increased deletions. This study included just 20 children, therefore further evidence is needed before this area can in considered for inclusion in the guideline. The study by Rose et al., 2014 was identified in the literature for the surveillance review. The study was excluded because an assessment of the abstract found no details of the study population examined or detailed study results to support the findings. The study by Essa et al., 2013 was also excluded from the surveillance because the abstract reported no data to support the study findings. The studies by Adams et al., 2013 and Alabdali et al., 2014 were not identified through the literature search for the surveillance review. Adams et al., 2013 reported that children with autism had higher levels of toxic metals in their blood and urine compared to typically developing children and that levels of several toxic metals are associated with variations in the severity of autism. The study was a small study including 55 children with autism compared to 44 controls and therefore further research to confirm the results in a larger population as well as research confirming an autism diagnosis from blood/urine tests for toxic metals would be pertinent. As such, additional evidence is needed before this area can be considered for inclusion in the guideline, however, NICE will continue to monitor this area at the next surveillance review of the guideline.

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			(Furuta et al., 2012). This paper identified that, in children with ASD, subtle or atypical symptoms might indicate the presence of constipation and that screening, identification, and treatment through a deliberate approach for underlying causes of constipation is appropriate. In individuals with autism, atypical presentations of common gastrointestinal problems can include emergence or intensifying of seemingly non-related 'autistic' behaviours such as self-harm, irritability, aggression, strange posturing or movements (Buie et al., 2010). In another paper published in Pediatrics the need for appropriate investigations was similarly highlighted: "Despite the magnitude of these issues, potential GI problems are not routinely considered in ASD evaluations. This likely reflects several factors, including variability in reported rates of GI disorders, controversies regarding the relationship between GI symptoms and the putative causes of autism, the limited verbal capacity of many ASD patients, and the lack of recognition by clinicians that certain behavioral manifestations in children with ASDs are indicators of GI problems (e.g. pain, discomfort, or nausea). Whether GI issues in this population are directly related to the pathophysiology of autism, or are strictly a comorbid condition of ASD remains to be determined, but clinical practice and research to date indicate the important role of GI conditions in ASDs and their impact on children as well as their parents and clinicians." (Coury et al., 2012). Analyses of the bacterial flora composition of individuals with ASD have frequently revealed the presence of abnormal bacteria that are	In terms of the study by Alabdali et al., 2014, this was published after the cut-off date for the surveillance review. The abstract reported that patients with autism spectrum disorder had significantly higher lead and mercury levels and lower glutathione-s-transferase activity and vitamin E concentrations compared with the controls, and there was a link between levels of these and autism severity. No detailed results were presented in the abstract or details of the study population including age group and numbers studied. Furthermore, the abstract does not discuss whether the tests confirmed a diagnosis of ASD in patients which would be needed before considering for inclusion in the guideline. NICE will continue to monitor this area at the next surveillance review of the guideline. The systematic review by Rossignol et al., 2014 was not identified through the literature search because it was published after the search cut-off date for the surveillance review. The abstract reported an association between toxicant exposures in the environment, such as air pollutants and pesticides, and increased ASD risk. There was weaker evidence relating to biomarkers of toxicants and ASD, including higher concentrations of heavy metals in blood, urine, hair, brain or teeth of children with ASD compared with controls. The abstract also reported on potential polymorphisms in genes associated with increased susceptibilities to toxicants. The abstract concluded that because of the limitations of many of the reviewed studies, additional evidence is needed to confirm the findings. As such, NICE considers that this new evidence is unlikely to impact on the

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			absent from healthy controls, as well as translocation of bacterial species to parts of gastrointestinal system that are not host to those bacteria in healthy individuals (De Angelis et al., 2013; Ekiel et al., 2010; Finegold et al., 2002; 2010; Parracho et al., 2005; Williams et al., 2012). Health professionals should consider the possibility of gastrointestinal dysfunction being present in some patients with ASD, especially in those presenting with strange posturing or movements, sleep disorders, food intolerances, and aggressive or self-injurious behaviours. There is currently very little awareness of these problems amongst health professionals, and such behaviours tend to be dismissed as 'just autism'. Guidelines should be amended to reflect this reality and reduce discrimination and lack of appropriate health care. 4. There is now substantial evidence that impaired energy metabolism and mitochondrial dysfunction, including brain energy metabolism, perturbation in sulfur and amino acid metabolism, high levels of oxidative stress and impaired methylation processes are more common in persons affected by autism than other groups, and could play a major pathological role in at least a subset of the disorder (Goh et al., 2014; Weissman et al., 2008). While cellular energy production in the brain is impaired in autism, elevations in oxidative stress as well as significantly reduced levels of glutathione and other cellular antioxidants have been found in many other areas of the body, including the immune cells such as leukocytes (Chauhan et al., 2012; Ghezzo et al., 2013; Gu et al., 2013;	guideline at this time but will continue to monitor this area at the next surveillance review of the guideline. The study by Frye et al., 2013 was not identified in the literature search for the surveillance review. The study included 213 children with ASD who underwent screening for metabolic disorders. The results reported in the abstract indicated that 17% of individuals with ASD demonstrated consistently abnormal acyl-carnitine panels, indicating mitochondrial dysfunction. Additional evidence is needed before this area can be considered for inclusion in the guideline, however, NICE will continue to monitor this area at the next surveillance review of the guideline. The study by Hadjixenofontos et al., 2013 was identified in the literature search for the surveillance review but was excluded because the abstract reported no data to support the study findings. The study by Calvo et al., 2014 was not identified through the literature search for the surveillance review because it was published after the search cut-off date. This was a case report of a patient with lathosterolosis and displayed autistic behaviours who, at 5 years follow-up after a liver transplant, had an arrest of mental deterioration. The study is beyond the scope of the guideline which is concerned with the recognition, referral and diagnosis of children and young people with autism. The study by Diaz-Stransky et al., 2012 was identified in the literature search for the surveillance review. The abstract presented a

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			Legido et al., 2013; Muratore et al., 2013; Napoli et al., 2014; Rose et al., 2012; 2014). Levels of oxidative stress and mitochondrial dysfunction correlated strongly with autism severity in one study, suggesting increased vulnerability to oxidative stress in those with more severe impairments (Essa at al., 2013). Correlation between severity of social and cognitive impairments and impaired detoxification mechanisms in ASD is further illustrated by preliminary findings of increased levels of several toxic metals and other environmental toxicants, as well as decreased activity of glutathione-S-transferase and lowered concentrations of vitamin E in children with ASD compared to typical controls (Adams, et al., 2013; Alabdali et al., 2014; Rossignol et al., 2014; Yorbik et al., 2010). A substantial percentage of patients with ASD display markers of abnormal mitochondrial energy metabolism, such as elevated lactate, pyruvate, and alanine in blood, urine and/or cerebrospinal fluid, as well as serum carnitine deficiency (Filipek et al., 2004; Frye et al., 2013; Oliveira et al., 2005). In the majority of cases this abnormal energy metabolism cannot be linked to genetic causes (Hadjixenofontos et al., 2013) or another primary inborn error of metabolism. However it is known that in many cases of metabolic diseases, such as urea cycle disorders, inborn errors of biopterin, or purine metabolism, autistic features may be a leading, or sometimes the only visible clinical feature of the underlying disease (Mayatepek, 2010). Abnormal cholesterol synthesis can also have autism as a presenting feature, and in some cases improvements in behavioural symptoms are noted following normalisation of cholesterol	commentary on the cognitive and behavioural aspects of Smith-Lemli-Opitz syndrome. The study was excluded from the surveillance review because it is out of scope of the guideline. **Risk factors** The guideline identified a number of risk factors for autism or ASD, including familiar and maternal factors. Prevalence of family history of autoimmune conditions was not identified in the guideline as one of the risk factors. The consultee highlighted the reference by Abisror et al., 2013 which was identified through the surveillance review. The abstract indicated that there was an increased risk of ASD in children born to mothers with antiphospholipid syndrome (APS). However, this study was excluded from the surveillance review because no data was presented in the abstract to support the findings. Furthermore, this was a small trial (36 children of mothers with APS) and therefore additional evidence would be needed before considering this risk factor for inclusion in the guideline. With regards to the heritability of autism, the study by Sandin et al., 2014 was not identified through the literature search because it was published after the search cut-off date for the surveillance review. The study was a population-based cohort study which found that individual risk of ASD and autistic disorder increased with increasing genetic relatedness. This is consistent with the guideline which lists a sibling with autism as one of the factors associated with an increased prevalence of autism. **Medical Investigations** The guideline considers the role of medical

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			metabolism (Calvo et al., 2014; Diaz-Stransky et al., 2012). In a study that screened 187 children with ASD, metabolic biomarkers were discovered in 7%, and for those 13 patients, treatment with biotin supplementation or institution of a ketogenic diet resulted in mild to significant clinical improvement in autistic features (Spilioti et al., 2013). In addition, cerebral folate deficiency, as well as autoantibodies to folate receptors, are suspected to play a pathological role in some cases of idiopathic autism because of their negative effects on cerebral folate metabolism and well-known involvement in other neurodevelopmental syndromes. Both of these conditions are often responsive to folinic acid therapy (Frye et al., 2012; Moretti et al., 2005; Ramaekers et al., 2012). The metabolic and chemical changes observed in ASD brains are suggestive of a dynamic disease process secondary to outside stressors (Corrigan et al., 2013; Tang et al., 2013). Health professionals should be made aware, via amended Guideline, of metabolic or mitochondrial dysfunction being present and contributing to autism etiology in some patients with ASD, even in the absence of primary inborn errors of metabolism or mitochondrial disease. ++++ Additional comment on the subject of autistic regression: Regarding developmental/autistic regressions, epileptic encephalopathy is mentioned, but attention also should be given to the	investigations that may identify causal conditions of autism and ASDs. The consultee highlighted three studies by Mostafa et al., 2012 and 2014 and Frye et al., 2012 relating to various antibodies in individuals with autism or ASD. In terms of the study by Mostafa et al., 2014, this was not identified through the literature search because it was published after the search cut-off date for the surveillance review. The study investigated serum anti-ds-DNA antibodies and seropositivity of anti-nuclear antibodies (ANA) in 100 autistic children in comparison to 100 healthy-matched children. The abstract reported that the frequencies of anti-ds-DNA antibodies and ANA in autistic children were significantly higher than that in healthy-matched children. The study by Mostafa et al., 2012 was also not identified through the literature search for the surveillance review. This study aimed to investigate the frequency of serum antineuronal auto-antibodies in 80 autistic children compared to 80 healthy-matched children. The abstract reported that the percentage of autistic children that tested positive for serum antineuronal antibodies was significantly higher than in healthy controls, and that the frequency of the antibodies was linked with severity of autism. Additional consistent evidence is needed before these areas can be considered in the guideline, particularly evidence relating to tests for specific antibodies which confirm a diagnosis of autism or ASD. NICE will continue to monitor these areas at the next surveillance review of this guideline. The study by Frye et al., 2012 was identified through the literature search for the surveillance review but was excluded because the abstract

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			following: there are an increasing number of reports of very defined circumstances—illuminated by detailed clinical investigations—around the reasons for such regression. These cases include the onset of Anti-N-Methyl-D-Aspartate (NMDA) receptor encephalitis and the recovery from autistic symptoms and neurological impairments following appropriate treatment (Creten et al., 2011; Gonzalez-Toro et al., 2013; Scott et al., 2013). Other circumstances involve encephalopathic illness of viral origin. While acute illnesses caused by a herpes virus, especially cytomegalovirus, are the most frequently reported ones (DeLong et al., 1981; Ghaziuddin et al., 2002; Gillberg, 1986; Libbey et al., 2005; Stubbs, 1978), there are also documented case reports of enterovirus encephalitis leading to autistic regression, including loss of previously acquired language and developmental milestones in a previously healthy toddler (Marques et al., 2014), as well as reports of autistic regressions, including late-onset ones, following malaria and pneumococcal meningoencephalitis (Baldaçara et al., 2011; Mankoski et al., 2006). Preliminary reports of prolonged steroid therapy improving long term outcomes in children with idiopathic autism lend weight to theories that inflammatory and/or immune-related processes play a causative role in autistic regression (Duffy et al., 2014). Unfortunately for patients and their families, in the vast majority of cases the circumstances of autistic regression, such as loss of speech and sudden behavioural regression, do not normally trigger medical inquiry. Guideline should be amended to reflect these findings of causes of regression following detailed medical investigation.	reported no detailed results confirming abnormal test results or a diagnosis of ASD as a result of the test. The study was also primarily focused on treatment of children with folate receptor autoantibodies which is out of scope of this guideline. The study by Spilioti et al., 2013 was highlighted relating to metabolic biomarkers for autism. This study was not identified through the literature search for the surveillance review. The results reported in the abstract indicated that metabolic screening found increased levels of 3-hydroxyisovaleric acid in the urine of 7% of a cohort of 187 children presenting with confirmed features of ASD. Due to the low numbers within the study, additional evidence is needed before this area can be considered for inclusion in the guideline. The study by Ramaekers et al., 2012 was identified through the literature search for the surveillance review but was excluded because an assessment of the abstract indicated that it was a commentary of existing evidence rather than a report of a study. The study by Corrigan et al., 2013 was identified through the literature search for the surveillance review. The abstract reported that grey matter chemical changes between 3 and 10 years of age differentiated children with ASD from those with developmental delay. The abstract provided no data to support the findings, therefore the study was excluded from the surveillance review. The study by Tang et al., 2013 was identified through the literature search for the surveillance review. The abstract reported evidence of

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			References: Abisror, N., Mekinian, A., Lachassinne, E., et al. (2013) Autism spectrum disorders in babies born to mothers with antiphospholipid syndrome. Semin Arthritis Rheum. Dec;43(3):348-51. Adams, J.B., Johansen, L.J., Powell, L.D., et al. (2011) Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. BMC Gastroenterol. 11: (1): 22. Adams, J.B., Audhya, T., McDonough-Means, S., et al., (2013) Toxicological status of children with autism vs. neurotypical children and the association with autism severity. Biol Trace Elem Res. Feb;151(2):171-80. doi: 10.1007/s12011-012-9551-1 Alabdali, A., Al-Ayadhi, L. and El-Ansary, A. (2014) A key role for an impaired detoxification mechanism in the etiology and severity of autism spectrum disorders. Behav Brain Funct. Anderson, D.K., Liang, J.W. and Lord, C. (2013) Predicting young adult outcome among more and less cognitively able individuals with autism spectrum disorders. J Child Psychol Psychiatry. Dec 9. Atladóttir, H.O., Pedersen, M.G., Thorsen, P., et al. (2009) Association of family history of autoimmune diseases and autism spectrum disorders. Pediatrics. Aug;124(2):687-94. Baldaçara, L., Diniz, T., Parreira, B., et al. (2011) Organic mental disorder after pneumococcal	mitochondrial dysfunction in children with ASDs but provided no data to support the findings. As such, the study was excluded from the surveillance review. **Regression** Thank you for your comments relating to autistic regression. The guideline does not currently recommend that health care professionals consider autistic regression following autoimmune and infectious encephalitis as a differential diagnoses or co-existing condition of autism. However, it does recommend that children and young people older than 3 years with regression in language, or children of any age with regression in motor skills, should be referred first to a paediatrician or paediatric neurologist. Two studies were identified by Gonzalez-Toro et al., 2013 and Scott et al., 2013 which reported case reports of individuals with anti-NMDA receptor encephalitis. The abstract for the study by Gonzalez-Toro et al. provided no information relating to autism/ASD which would impact on any of the guideline recommendations. The study by Scott et al. was excluded from the surveillance review because no data was presented in the abstract to support the study findings of an improvement in language, social skills and movements as a result of treatment. The study concluded that cases of anti-NMDA receptor encephalitis should be suspected as the cause of autistic regression. The study by Marques et at., 2014 was not identified through the literature search because it was published after the search cut-off date for the surveillance review. The abstract reported a

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			meningoencephalitis with autism-like symptoms. Rev Bras Psiquiatr. Dec;33(4):410-1. Barrett B., Byford S., Sharac J., et al. (2012) Service and wider societal costs of very young children with autism in the UK. J Autism Dev Disord. May;42(5):797-804. Buie, T., Campbell, D.B., Fuchs, G.J., et al. (2010a) Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. Pediatrics. 125: Suppl 1: S1-S18. Buie, T., Fuchs, G.J., Furuta, G.T., et al. (2010b) Recommendations for evaluation and treatment of common gastrointestinal problems in children with ASDs. Pediatrics. 125 Suppl 1: S19-S29. Calvo P.L., Brunati, A., Spada, M., et al. (2014) Liver Transplantation in Defects of Cholesterol Biosynthesis: The Case of Lathosterolosis. Am J Transplant. Mar 12. Chaidez, V., Hansen, R.L. and Hertz-Picciotto, I. (2013) Gastrointestinal Problems in Children with Autism, Developmental Delays or Typical Development. J Autism Dev Disord. Nov 6. Chauhan, A., Audhya, T. and Chauhan, V. (2012) Brain region-specific glutathione redox imbalance in autism. Neurochem Res. 1-9 Chen, M.-H., Su, T.-P., Chen, Y.-S., et al. (2013) Comorbidity of allergic and autoimmune diseases in patients with autism spectrum disorder: A nationwide population-based study. Res Autism Spect Dis. 7: (2): 205-212.	case study of a toddler with enterovirus encephalitis leading to an autism spectrum disorder. Following an assessment of the abstract, it was considered that further large-scale studies would be needed relating to autistic regression following autoimmune and infectious encephalitis to be considered for inclusion in the guideline. The study by Duffy et al., 2014 was not identified through the literature search because it was published after the search cut-off date for the surveillance review. The abstract reported that steroid therapy led to an improvement in regressive autism in children compared to non-treated ASD children. Treatment is out of scope of this guideline, therefore this would not impact on any of the guideline recommendations. The following references were not identified through the literature search because they were published prior to search cut-off date for the surveillance review (29th October 2012 - 29th January 2014: • Atladóttir et al., 2009 • Baldaçara et al., 2011 • Barrett et al., 2012 • Buie et al., 2010a • Buie et al., 2010b • Chauhan et al., 2012 • Creten et al., 2011 • DeLong et al., 1981 • de Magistris et al., 2010 • Ekiel et al., 2010 • Filipek et al., 2004 • Finegold et al., 2002 • Finegold et al., 2010 • Ghaziuddin et al., 2002

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			Corrigan, N.M., Shaw, D.W., Estes, A.M., et al. (2013) Atypical developmental patterns of brain chemistry in children with autism spectrum disorder. JAMA Psychiatry. Sep;70(9):964-74. Coury, D.L., Ashwood, P., Fasano, A., et al. (2012) Gastrointestinal conditions in children with autism spectrum disorder: developing a research agenda. Pediatrics. 130: (Supplement 2): S160-S168. Creten, C., van der Zwaan, S., Blankespoor, R.J., et al. (2011) Late onset autism and anti-NMDA-receptor encephalitis. Lancet. Jul 2;378(9785):98. Croen, L.A., Zerbo, O., Qian, Y., et al., (2014) Psychiatric and Medical Conditions Among Adults with ASD. https://imfar.confex.com/imfar/2014/webprogram/Paper17783.html De Angelis, M., Piccolo, M., Vannini, L., et al. (2013) Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. PLoS One. 2013 Oct 9;8(10):e76993. DeLong, G.R., Bean, S.C. and Brown, F.R. (1981) Acquired reversible autistic syndrome in acute encephalopathic illness in children. Arch Neurol. Mar;38(3):191-4. de Magistris, L., Familiari, V., Pascotto, A., et al. (2010) Alterations of the intestinal barrier in patients with autism spectrum disorders and in their first-degree relatives. J Pediatr Gastroenterol Nutr. 51: (4): 418.	• Gillberg, 1986 • Goldson et al., 2007 • Gurney et al., 2006 • Hallmayer et al., 2011 • Horvath et al., 1999 • Jones et al., 2008 • Kohane et al., 2012 • Kushak et al., 2011 • Lea et al., 2012 • Libbey et al., 2005 • Liptake et al., 2006 • Mankoski et al., 2006 • Mayatepek, 2010 • Moretti et al., 2005 • Mostafa et al., 2008 • Oliveira et al., 2005 • Olivié, 2012 • Parracho et al., 2005 • Pellicano, 2012 • Rose et al., 2012 • Schieve et al., 2012 • Schurman et al., 2012 • Smith et al., 2012 • Stubbs et al., 1980 • Sweeten et al., 2003 • Torrente et al., 2004 • Tregnago et al., 2012 • Wang et al., 2011 • Wang et al., 2012 • Weissman et al., 2008 • Williams et al., 2011 • Williams et al., 2012 • Yap et al., 2010 • Yorbik et al.,2010

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			de Magistris, L., Picardi, A., Siniscalco, D., et al. (2013) Antibodies against food antigens in patients with autistic spectrum disorders. Biomed Res Int. 2013:729349. Diaz-Stransky, A. and Tierney, E. (2012) Cognitive and behavioral aspects of Smith-Lemli-Opitz syndrome. Am J Med Genet C Semin Med Genet. Nov 15;160C(4):295-300. Duffy, F.H., Shankardass, A., McAnulty, G.B., et al. (2014) Corticosteroid therapy in regressive autism: a retrospective study of effects on the Frequency Modulated Auditory Evoked Response (FMAER), language, and behavior. BMC Neurol. May 15;14(1):70. Ekiel, A., Aptekorz, M., Kazek, B., et al. (2010) Intestinal microflora of autistic children. Med Dosw Mikrobiol. 2010;62(3):237-43. Essa, M.M., Braidy, N., Waly, M.I., et al. (2013) Impaired antioxidant status and reduced energy metabolism in autistic children. Res Autism Spect Dis. Volume 7, Issue 5, May, Pages 557–565. Fein, D., Barton, M., Eigsti, I.M., et al. (2013) Optimal outcome in individuals with a history of autism. J Child Psychol Psychiatry. 54: (2): 195-205. Filipek, P.A., Juranek, J., Nguyen, M.T., et al. (2004) Relative carnitine deficiency in autism. J Autism Dev Disord. 34: (6): 615-623. Finegold, S.M., Molitoris, D., Song, Y., et al. (2002) Gastrointestinal microflora studies in late-	

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			onset autism. Clin Infect Dis. 35: (Suppl 1): S6-S16. Finegold, S.M., Dowd, S.E., Gontcharova, V., et al. (2010) Pyrosequencing study of fecal microflora of autistic and control children. Anaerobe. 16: (4): 444-453. Frye, R., Sequeira, J., Quadros, E., et al. (2012) Cerebral folate receptor autoantibodies in autism spectrum disorder. Molecular Psychiatr. Jan 10. Frye, R.E., Melnyk, S. and MacFabe, D.F. (2013a) Unique acyl-carnitine profiles are potential biomarkers for acquired mitochondrial disease in autism spectrum disorder. Transl Psychiatry. 3: (1): e220. Furuta, G.T., Williams, K., Kooros, K., et al. (2012) Management of Constipation in Children and Adolescents With Autism Spectrum Disorders. Pediatrics. 130: (Supplement 2): S98-S105. Ghaziuddin, M., Al-Khouri, I. and Ghaziuddin, N. (2002) Autistic symptoms following herpes encephalitis. Eur Child Adolesc Psychiatry. Jun;11(3):142-6. Ghezzo, A., Visconti, P., Abruzzo, P.M., et al. (2013) Oxidative Stress and Erythrocyte Membrane Alterations in Children with Autism: Correlation with Clinical Features. PLoS One. Jun 19;8(6):e66418. Gillberg, C. (1986) Onset at age 14 of a typical autistic syndrome. A case report of a girl with herpes simplex encephalitis. J Autism Dev Disord. Sep;16(3):369-75.	

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			Genet. Jan;77(1):9-21. Hallmayer, J., Cleveland, S., Torres, A., et al. (2011) Genetic heritability and shared environmental factors among twin pairs with autism. Arch of Gen Psych., 68: (11): 1095. Horvath, K., Papadimitriou, J.C., Rabsztyn, A., et al. (1999) Gastrointestinal abnormalities in children with autistic disorder. J Pediatr. 135: (5): 559-563. Isaksen, J., Bryn, V., Diseth, T.H., et al. (2012) Children with autism spectrum disorders–The importance of medical investigations. Eur J Paediatr Neurol. Jones, S., Howard, L., Thornicroft, G. (2008) 'Diagnostic overshadowing': worse physical health care for people with mental illness. Acta Psychiatr Scand. Sep;118(3):169-71 Kohane, I.S., McMurry, A., Weber, G., et al. (2012) The Co-Morbidity Burden of Children and Young Adults with Autism Spectrum Disorders. PloS One. 7: (4): e33224. Kushak, R.I., Lauwers, G.Y., Winter, H.S., et al. (2011) Intestinal disaccharidase activity in patients with autism. Effect of age, gender, and intestinal inflammation. Autism. 15: (3): 285-294. Lea, C.L., Sauven, N. and Thorpe, M.P.B. (2012) Explaining the Unexplained: How Far to Investigate Symptoms in Learning Disabled Patients?. Arch Dis Child. 97. A137. Legido, A., Jethva, R. and Goldenthal, M.J.	

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			(2013) Mitochondrial dysfunction in autism. Semin Pediatr Neurol. 20(3):163-75. Libbey, J.E., Sweeten, T.L., McMahon, W.M., et al. (2005) Autistic disorder and viral infections. J Neurovirol. 2005;11: 1-10. Liptak, G.S., Stuart, T. and Auinger, P. (2006) Health care utilization and expenditures for children with autism: data from U.S. national samples. J Autism Dev Disord. Oct;36(7):871-9. Mankoski, R.E., Collins, M., Ndosi, N.K., et al. (2006) Etiologies of autism in a case-series from Tanzania. J Autism Dev Disord. Nov;36(8):1039-51. Marques, F., Joao Brito, M., Conde, M., et al. (2014) Autism Spectrum Disorder Secondary to Enterovirus Encephalitis. J Child Neurol. May 2014 vol. 29 no. 5 708-714. Mayatepek, E. (2010) Inherited Metabolic Diseases. In: Hoffmann G. et al. eds. Psychiatric Disease. Springer Berlin Heidelberg. Mazefsky, C.A., Schreiber, D.R., Olino, T.M., et al. (2013) The association between emotional and behavioral problems and gastrointestinal symptoms among children with high-functioning autism. Autism. Oct 8. Mazurek, M.O., Vasa, R.A., Kalb, L.G., et al. (2012) Anxiety, Sensory Over-Responsivity, and Gastrointestinal Problems in Children with Autism Spectrum Disorders. J Abn Child Psych.	

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			McElhanon, B.O., McCracken, C., Karpen, S., et al. (2014) Gastrointestinal Symptoms in Autism Spectrum Disorder: A Meta-analysis. Pediatrics. Apr 28. Ming, X., Stein, T.P., Barnes, V., et al. (2012) Metabolic perturbance in autism spectrum disorders: A metabolomics study. J Proteome Res. 11: (12): 5856-5862. Moretti, M.D., Sahoo, T. and Hyland, K. (2005) Cerebral folate deficiency with developmental delay, autism, and response to folinic acid. Neurology. March 22, vol. 64. no. 6. 1088-1090 Mostafa, G.A., Hamza, R.T. and El-Shahawi, H.H. (2008) Allergic manifestations in autistic children: Relation to disease severity. J of Ped Neurol. 6, pp. 115–123. Mostafa, G.A. and Al-Ayadhi, L.Y. (2012) The relationship between the increased frequency of serum antineuronal antibodies and the severity of autism in children. Eur J Paed Neurology. 16(5):464-8. Mostafa, G.A., El-Sherif, D.F and Al-Ayadhi, L.Y. (2014) Systemic auto-antibodies in children with autism. J Neuroimmunol. Mukaddes, N.M., Tutkunkardaş, M.D., Sari, T.O., et al. (2014) Characteristics of children who lost the diagnosis of autism: A sample from Istanbul, Turkey. Aut Res Treat. Article ID 472120 Muratore, C.R., Hodgson, N.W., Trivedi, M.S., et al. (2013) Age-dependent decrease and	

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			Peters, B., Williams, K.C., Gorrindo, P., et al. (2013) Rigid-Compulsive Behaviors are Associated with Mixed Bowel Symptoms in Autism Spectrum Disorder. J Autism Dev Disord. Ramaekers, V., Sequeira, J.M. and Quadros, E.V. (2012) Clinical recognition and aspects of the cerebral folate deficiency syndromes. Clin Chem Lab Med. Dec 20:1-15. Rose, S., Melnyk, S., Pavliv, O., et al. (2012) Evidence of oxidative damage and inflammation associated with low glutathione redox status in the autism brain. Transl Psychiatry. 2: (7): e134. Rose, S., Frye, R.E., Slattery, J., et al. (2014) Oxidative stress induces mitochondrial dysfunction in a subset of autism lymphoblastoid cell lines in a well-matched case control cohort. PLoS One. Rossignol, D.A., Genuis, S.J. and Frye, R.E. (2014b) Environmental toxicants and autism spectrum disorders: a systematic review. Transl Psychiatry. Feb 11;4:e360. Sandin, S., Lichtenstein, P., Kuja-Halkola, R., et al. (2014) The Familial Risk of Autism. JAMA. 311(17):1770-1777. Schieve, L.A., Gonzalez, V., Boulet, S.L., et al. (2012) Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006–2010. Res Dev Dis. 33: (2): 467-476. Schurman, J.V., Friesen, C.A., Dai, H., et al.	

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			Tang, G., Gutierrez Rios, P., Kuo, S.H., et al. (2013) Mitochondrial abnormalities in temporal lobe of autistic brain. Neurobiol Dis. Jun;54:349-61. Torrente, F., Anthony, A., Heuschkel, R.B. et al. (2004) Focal-enhanced gastritis in regressive autism with features distinct from Crohn's and Helicobacter pylori gastritis. Am J Gastroenterol.;99 :598– 605. Treating Autism Survey (2014) Treating Autism. Available through mail@treatingautism.co.uk Tregnago, M.K. and Cheak-Zamora N.C. (2012) Systematic review of disparities in health care for individuals with autism spectrum disorders in the United States. Res Autism Spectrum Dis. Volume 6, Issue 3, July–Sept, 1023–1031. Venkat, A., Jauch, E., Russell, W.S., et al. (2012) Care of the patient with an autism spectrum disorder by the general physician. Postgrad Med J. Aug;88(1042):472-81. Walker, S.J., Fortunato, J., Gonzalez, L.G. et al. (2013) Identification of unique gene expression profile in children with regressive autism spectrum disorder (ASD) and ileocolitis. PLoS One. 2013;8(3):e58058. Wang, L.W., Tancredi, D.J. and Thomas, D.W. (2011) The prevalence of gastrointestinal problems in children across the United States with autism spectrum disorders from families with multiple affected members. J Develop Behav Ped. 32: (5): 351-360.	

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			Wang, L., Christophersen, C.T., Sorich, M.J., et al. (2012) Elevated fecal short chain fatty acid and ammonia concentrations in children with autism spectrum disorder. Dig Dis Sci. Aug;57(8):2096-102. Weissman, J.R., Kelley, R.I., Bauman, M.L., et al. (2008) Mitochondrial disease in autism spectrum disorder patients: a cohort analysis. PLoS One. 3(11):e3815. Williams, B.L., Hornig, M., Buie, T., et al. (2011) Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PloS One. 6: (9): e24585. doi: 10.1371/journal.pone.0024585 Williams, B.L., Hornig, M., Parekh, T., et al. (2012) Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of Sutterella species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. MBio. 3: (1). Yap, I.K., Angley, M., Veselkov, K.A., et al. (2010) Urinary metabolic phenotyping differentiates children with autism from their unaffected siblings and age-matched controls. J Proteome Res. 9: (6): 2996-3004. Yorbik, O., Kurt, I., Haşimi, A., et al. (2010) Chromium, cadmium, and lead levels in urine of children with autism and typically developing controls. Biol Trace Elem Res. Jun;135(1-3):10-5.	
Flynn	Disagree		This guideline (CG128) requires updating to	Thank you for your comments.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Pharma	Areas for update are as follows: CG128 Introduction		reflect modern clinical practice and the subsequent shift in thinking allowing for a co-diagnosis of ASD and ADHD as comorbid conditions. The release of the American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Fifth Edition (May, 2013), the move towards Autism Spectrum Disorder (ASD) and the important new provision within, supporting clinicians in making a comorbid diagnosis of clinical conditions such as ADHD with autism spectrum disorders warrant both update and inclusion in a revised CG128 clinical guideline. Rationale for update are as follows: Autism spectrum disorders (ASD) are diagnosed in children, young people and adults where certain behaviours meet the criteria defined in the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders DSM-IV Fourth Edition (DSM-IV) and have a significant impact on function. The updated and revised Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Fifth Edition has been launched (May, 2013). Implementation and uptake of the revised criteria is on-going globally in both the clinical and the research setting and as such, authoritative UK clinical guidance should be updated to reflect the changes to the diagnostic criteria, particularly areas where there have been significant clinical change such as acknowledgement and acceptance of the co-existence of ASD with other conditions making comorbid diagnoses of ASD with ADHD possible.	The guideline recommends that health care professionals should consider whether the child or young person may have a coexisting condition, including ADHD, and if suspected carry out appropriate assessments and referrals. The new evidence relating to coexisting conditions with autism which was identified through the 4 year surveillance review supported this recommendation. New evidence relating to DSM-5 was identified through the surveillance review. However, as the criteria were only published in 2013, there is limited evidence available relating to DSM-5 and therefore it is not currently clear what potential impact that this may have on the guideline. As such, this guideline will remain on the active surveillance list and this area will be monitored at the next surveillance review of the guideline. Furthermore, it is currently recommended 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.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
	Section 1.5.5		Clinicians should be encouraged and supported to use 'current' diagnostic criteria, assessing behavioural features in-line with DSM-5, which benefits from up to date research and understanding of autism rather than continuing to use the dated DSM-IV which has significant flaws relevant to the accurate diagnosis of patients with autism e.g. precluding the presence of common comorbid conditions like ADHD	
	Section 1.57		Due to the high prevalence of a range of comorbid conditions such as ADHD occurring in patients with ASD, the emphasis of the clinical guideline should be on ensuring appropriate diagnoses can be made. Comorbid diagnoses are possible and may be achieved for ASD and the conditions outlined within DSM-5, rather than currently seeking to exclude ADHD as a comorbid condition as DSM-IV does	
	Section 1.5.10		The comments outlined in this section are out of date as the DSM-IV diagnostic criteria have now been superseded by DSM-5 (May, 2013).	
	Section 1.5.12		Making an accurate diagnosis of autism in some patients, particularly in the presence of a comorbid condition (such as ADHD) is difficult; this is exacerbated with DSM-IV promoting a diagnosis of exclusion. Inclusion and incorporation of the updated DSM-5 diagnostic criteria into routine clinical practice allows the clinician the possibility (and indeed the probability) of the presence of comorbid conditions (one or more) being present when making a diagnosis.	
	Section 1.5.15		The current guideline acknowledges the coexistence of comorbid conditions such as ADHD and ASD in patients. It would be more	

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			appropriate to reference and incorporate the relevant section(s) of DSM-5 which support and assists clinicians in making these comorbid diagnoses, and support commissioners in understanding service requirements, for more complex patients such as those with comorbid ADHD and ASD	
	Surveillance Review CG128		Rationale for update are as follows:	
	Diagnostic assessment: What should be the components of the diagnostic assessment?		Whilst new and alternative tools to support rapid and accurate diagnosis of ASD are explored, for the purposes of diagnosis it is critical to update the guideline (CG128) to include the updated Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Fifth Edition, in much the same way DSM-IV and ICD-10 are currently recommended in making and supporting a diagnosis in the current guideline. It is particularly important to include the updated diagnostic criteria as they support the presence of comorbid conditions such as ADHD with ASD. The ability to make a diagnosis of comorbid ADHD in the presence of ASD is important for clarity for both clinicians and commissioners, to ensure patients receive the appropriate treatment and referral.	
	Clinical area: Which are the common coexisting conditions that should be considered as part of assessment?		The current guideline makes an allowance for the diagnosis of autism with a range of comorbid conditions (such as ADHD); the acceptance of comorbid diagnoses would be further supported by inclusion of the diagnostic criteria outlined in DSM-5, where the presence of a range of comorbidities are described in the diagnostic criteria. The exclusion of DSM-5 and the continued use of DSM-IV, may lead to confusion and/or conflict between clinicians and	

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	Conclusion		commissioners: clinicians may be required to make a comorbid diagnosis however, use of DSM-IV criteria does not make provision for such a diagnosis (ASD and ADHD). This may affect not only the making of an accurate diagnosis but may inhibit treatment, referral and support of patients suffering with comorbid conditions. The American Psychiatric Association has updated their diagnostic criteria and these are being incorporated in modern medicine and into psychiatric diagnosis. Whilst understanding that some aspects of the up-dated criteria outlined in DSM-5 may have an untoward impact on the treatment of patients with autism, the decision to delay the inclusion of DSM-5 for minimally a further 2 years (and 3 years since launch) may well also lead to disadvantages in care and diagnosis for a range of patients, particularly those suffering from autism with comorbid conditions such as ADHD.	
The Royal College of Psychiatrists	Disagree		There needs to be further discussion on moving on from diagnosis and the possibility of support on behavioural/psychiatric issues. Even if it is beyond the scope of this document to detail provision there should be acknowledgment that making the diagnosis is only the first step. That many children (and adults) go on to develop significant problems with behaviour and mental health that need to be addressed by services. The document also quite rightly emphasised the need for developing pathways for diagnosis. Assuming that most people should have done this by now should it not state would should be in place for each area. The actual information on making the diagnosis and the importance of co-morbidity is excellent.	Thank you for your comments. As you have highlighted, the provision of interventions and support for children and young people with autism is beyond the scope of this guideline and is covered separately by CG170 - the management and support of children and young people on the autism spectrum. CG170 covers the second part of the care pathway. Together, CG170 and CG128 provide guidance on the full range of care for children and young people with autism: case identification, assessment and diagnosis; management; and support for children and young people, their families and other carers, and transition to adult services. This is illustrated in full in the NICE Pathway for Autism.
Planet	Disagree		Comments on proposal not to update the	Thank you for your comments.

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
Autism			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? Autism may be underdiagnosed in girls is vague and does not specify what differences should be looked for. As you have recognised "Children with higher communication capabilities were also diagnosed at an older age." and this needs addressing. Regarding the comment "mothers with depression had higher scores on the Social Responsiveness Scale (SRS)" this could well be due to the mothers being on the spectrum themselves and undiagnosed. 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? Clinical tools are still relied on too heavily by many clinicians, the ADOS-2 is only 77% clinically reliable in high-functioning individuals. The concern is that the ADOS:2 is widely touted as the gold standard tool and is used by many clinicians. The NICE advice that tools ought not to be relied upon is being ignored by many clinicians. 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 The problem here is that with the blame culture	<u>Signs and symptoms</u> The guideline states that autism is under-diagnosed in girls which was based on the GDG's clinical experience. However, this issue was not addressed in the systematic review of the evidence during guideline development. The new evidence identified through the 4 year surveillance review was heterogeneous in relation to the differences between boys and girls, therefore it was considered unlikely that this evidence would impact on the current guideline recommendation. The guideline recommends that every autism diagnostic assessment should include assessment of social and communication skills and behaviours. Failure to follow the guidance recommendations is a local implementation issue. With regards to mothers with depression with higher scores on the Social Responsiveness Scale and potential for them being under-diagnosed, this would be outside the scope of this guideline. <u>Following referral/Diagnostic assessment: tools</u> Through the surveillance review, a number of assessment tools specific to autism were identified in the new evidence. This evidence was consistent with the guideline recommendations which state: do not rely on any autism-specific diagnostic tool alone to diagnose autism. Failure to follow the guidance recommendations is an implementation issue. <u>Diagnostic assessment: Biomedical investigations</u>

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			existing in state services, much of the time when parents seek help for their child's difficulties, parenting is often looked to, as opposed to getting on with assessing the child for autism. That is the reason that children from certain backgrounds are getting diagnosed later. 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) Clinical tools are still relied on too heavily by many clinicians, the ADOS-2 is only 77% clinically reliable in high-functioning individuals. The concern is that the ADOS-2 is widely touted as the gold standard tool and is used by many clinicians. The NICE advice that tools ought not to be relied upon is being ignored by many clinicians. This is further shown by the statement "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" in the question: “Q. What is the agreement of an autism diagnosis across different diagnostic tools? “	A number of studies were identified in the surveillance review relating to different biomedical investigations for diagnosis of autism, including neuroimaging. The new evidence was variable and therefore it was not considered to impact on the recommendation 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. With regards to the study examining whether specific brain networks can differentiate between children with ASD and typically developing children, this was a small study of just 20 children. Additional evidence would be needed before this could be considered for inclusion within the guideline. <u>Diagnostic assessment: stability of a diagnosis</u> No specific evidence was provided by the consultee. However, the guideline does recommend that 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. <u>Assessment of co-existing conditions</u> The guideline recommends that health care professionals should consider whether the child or young person may have a coexisting condition, including ADHD, and if suspected carry out appropriate assessments and referrals. The new evidence relating to coexisting conditions with autism which was identified through the 4 year surveillance review supported this recommendation. Failure to follow the guideline recommendations is a local

Stakeholder	Do you agree that the guidance should not be updated?	Comments on equality issues or areas excluded from the original scope	Comments If you disagree please explain why	Response
			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. The advice to consider the necessity for EEGs and other tests according to the individual is not something that clinicians seem to even be aware of, let-alone following. Regarding the tests of brain networks, as the findings were so high (75% and 80%) surely this should be recommended as standard? Clinical area: Diagnostic assessment Q. What is the stability of an autism diagnosis over time? Autism is a lifelong condition. It is also a spectrum. The presentation of the condition varies according to the individual's environment. if they are in a supportive environment it can seem there are no significant traits but they can regress very quickly when put into an inconducive environment and this needs to be written into the guidelines. 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 This is another example of the reality not being reflected by the Guidelines. Certainly in our health authority such co-existing diagnoses are	implementation issue. Thank you for highlighting the studies/articles relating to hypermobility syndrome/Ehlers Danlos Syndrome and ASD. The studies by Eccles et al, 2012 and Sieg, 1992 were not identified through the surveillance review because they published prior to the literature search start date for this review. The online blog by Dr.Manuel Casanova was also not identified by the surveillance review as it does not fit the criteria for evidence for inclusion in our surveillance process. With regards to discrimination against females in the assessment and diagnosis of autism, the guideline currently recommends that when considering the possibility of autism, health care professionals should be aware that autism may be under-diagnosed in girls. Issues regarding the implementation of this recommendation are beyond the remit of the surveillance review.

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			not considered as standard. 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 There is growing awareness of a link between hypermobility syndrome/Ehlers Danlos Syndrome and ASD http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3365276/, http://www.ncbi.nlm.nih.gov/pubmed/1537777, http://www.sciencedirect.com/science/article/pii/S0890856709644300, http://corticalchauvinism.com/2013/08/12/ehlers-danlos-syndrome-and-autism/. I know anecdotally of several families with both conditions and have read a lot of anecdotal evidence of others with both conditions. It is not routinely tested for and being another invisible disability is going unnoticed. Since there are many parents with autism and/or EDS being falsely accused of child abuse due to ignorance about both conditions it is vital that EDS is a routinely assessed for with ASC assessment. Anti-discrimination and equalities considerations None identified. This is clearly wrong. There is great discrimination against females being assessed and diagnosed with ASC. There is much information out there about this. Three females	

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			in my own family are autistic, two struggled greatly to get diagnosis. Why do guidelines not influence the ICD11 that is being drafted to be updated to take female ASC presentation into account? The DSM has already failed abysmally on that front, quite apart from removing Asperger's as a diagnosis.	
British Academy of Childhood Disability	Agree		Members of BACD agree that there is insufficient new evidence to justify updating this guideline now.	Thank you for your comment.
Department of Health			The Department of Health has no substantive comments to make, regarding this consultation	Thank you.
Royal College of Nursing			The Royal College of Nursing have no comments to submit to inform on the above review surveillance consultation.	Thank you.
NHS England			NHS England has no substantive comments to make regarding this consultation.	Thank you.
Royal College of Paediatrics and Child Health			We have not received any responses for this consultation.	Thank you.

Appendix 2 Decision matrix

The table below provides summaries of the evidence for key questions for which studies were identified.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
128-01a: What are the signs and symptoms that should prompt a healthcare professional or other professional in any context to think of autism?			
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	<u>Pre-school children (0–5 years)</u> 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	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.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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 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	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%).		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
developing children.			
128-01b: When should a child or young person be referred for diagnostic assessment?			
No new evidence identified.	No new evidence identified.	None identified	No relevant evidence identified.
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?			
128-02a: Are there tools to identify an increased likelihood of autism that are effective in assessing the need for specialist autism assessment?			
<u>Manchester Inventory for Playground Observation (MIPO)</u> 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. <u>SSI</u> 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. <u>CSI-4</u>	<u>Autism-spectrum quotient</u> 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. <u>Child Behaviour Checklist</u> 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	One GDG member reported that there is more evidence on screening tools but it is unlikely to 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.	A number of different tools to identify an increased likelihood of autism were identified in the new 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.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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 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.	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%.		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<u>M-CHAT</u> 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. <u>PreAut Grid</u> 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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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. <u>Toddler autism screening questionnaire</u>		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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. <u>SIQ</u> 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%. <u>First Year Inventory</u> 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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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.		
128-02b: 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)**			
<u>Socioeconomic factors</u> 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. <u>Familiar or parental factors</u> A study[37] of 214 children with a previous diagnosis of autism spectrum disorder found that children of mothers with	<u>All factors</u> 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	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 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,

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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.	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		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.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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.		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	<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.		
128-02b: 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)**			
No evidence identified.	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.	None identified.	The new evidence is consistent with the current evidence in the guideline which identifies 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 associated factors, including Neurofibromatosis, should be included in the referral letter to the autism team.
128-02c: 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?			
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	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

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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.			and young people in the criminal justice system.
128-03: What should be the components of the diagnostic assessment? When should they be undertaken, in what subgroups and in what order?			
128-03a: 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)			
Q-CHAT and AQ One study[80] aimed to determine whether 10 items 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. ADI-R 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	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	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 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.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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 was 81%; and in the phrase-speech group the sensitivity was 80% and specificity was 70%. <u>ADOS</u> 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–	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. <u>ADOS</u> 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. <u>ADOS/ADI-R</u> 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. <u>CASS</u>		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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	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-		

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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.	Standard Version (CARS2-ST) for the Lebanese population found that the tool had good reliability and internal consistency when assessing for ASD in children.		
128-03b: 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.			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
128-03c: biomedical investigations for diagnosis of autism, for example electroencephalography (EEG), brain scan, genetic tests, counselling; investigations for associated medical conditions.			
<u>EEG</u> 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. <u>Genetic tests</u> 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 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	<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	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.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
tests normal, compared to 97% if no dysmorphic features were present.	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		

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	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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.		

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	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.		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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. Genetic tests 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		

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	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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.		
128-04a: What are the most important differential diagnoses of autism?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
128-04b: What features observed during diagnosis reliably differentiate other conditions from autism?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
128-05: How should information be integrated to arrive at diagnosis?			
128-05a: Is the diagnostic assessment more accurate and reliable when performed by a multidisciplinary team or a single practitioner?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
128-05b: What is the stability of an autism diagnosis over time?			
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	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	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 and 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

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
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 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.	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 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.		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. 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.
128-05c: What is the agreement of an autism diagnosis across different diagnostic tools?			

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
No new evidence identified.	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% 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	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.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	participants met DSM-5 criteria when using combined data from both tools.		
128-06: How should the findings of the diagnostic assessment be communicated to children and young people, and their families/carers?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
128-07: What actions should follow assessment for children and young people who are not immediately diagnosed with autism?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
128-08: 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**			
No new evidence identified.	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 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.	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.
○ **mental and behavioural disorders, such as attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), anxiety, depression, Tourette, tic disorders**			
No new evidence identified.	A study[143] was identified which utilised DSM-IV-referenced rating scales to	None identified.	The evidence relating to co-existing mental and behavioural conditions, including ADHD

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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 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.		and anxiety disorders is consistent with the conditions identified in the guideline.
○ **medical or neurological problems such as functional gastrointestinal problems, tuberous sclerosis, neurofibromatosis**			
No new evidence identified.	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	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

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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 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		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.

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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		

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
	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%).		
128-09: What information do children and young people, and their families/carers, need during the process of referral, assessment and diagnosis of autism?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
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?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
Research recommendations			
RR 1: 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?			
No new evidence identified.	An observational study[169] 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. 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.	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 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.
RR 2: 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 identified.	No new evidence identified.	None identified.	No relevant evidence identified.
RR 3: Do additional assessments (for IQ, language ability and motor ability) improve accuracy in diagnosing autism among preschool children (younger than 5			

Conclusions from Evidence Update (2013)	Is there any new evidence/intelligence identified during this 4-year surveillance review (2014) that may change this conclusion?	Clinical feedback from the GDG	Conclusion of this 4-year surveillance review (2014)
years) compared with signs and symptoms alone?			
No new evidence identified.	No new evidence identified.	None identified.	No relevant evidence identified.
RR 4: 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 identified.	No new evidence identified.	None identified.	No relevant evidence identified.

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