



2021 exceptional surveillance of suspected cancer: recognition and referral (NICE guideline NG12) and suspected neurological conditions: recognition and referral (NICE guideline NG127)

Surveillance report

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Surveillance decision

We will refresh the [NICE guidelines on suspected cancer](#) and [suspected neurological conditions](#) to cross-reference recommendations between the guidelines on referrals for children with an absent red reflex, with or without a new-onset squint, so that users are clear under what circumstances a referral should be urgent or immediate. We will also amend the [rationale for recommendation 1.30.1 in the NICE guideline on suspected neurological conditions](#) to clarify that immediate referral is recommended due to the potential neurological conditions in addition to retinoblastoma that may be associated with an absent red reflex with a new-onset squint.

Reason for the exceptional review

We received an external enquiry asking why there was a difference between recommendations on referral times for children with an absent red reflex between the NICE guidelines on suspected cancer and suspected neurological conditions:

- [Recommendation 1.12.2 in the NICE guideline on suspected cancer](#) says to 'Consider [urgent](#) referral (for an appointment within 2 weeks) for ophthalmological assessment for retinoblastoma in children with an absent red reflex'.
- [Recommendation 1.30.1 in the NICE guideline on suspected neurological conditions](#) says to '[Refer immediately](#) children with new-onset squint that occurs together with loss of red reflex in one or both eyes to ophthalmology services'. 'Refer immediately' is defined as being seen by the specialist service within a few hours, or even more quickly if necessary.

This exceptional review explores the reasons for the difference between the referral times recommended between these recommendations.

Methods

The exceptional surveillance process consisted of:

- Considering the evidence used to develop the guidelines.
- Examining related NICE guidance.

- Feedback from topic experts.
- Examining the NICE event tracker for relevant ongoing and published events (no events were identified).
- Assessing the topic expert feedback against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

We decided that full updated literature searches were not needed because the information we had from guideline development and topic experts was enough to establish whether an update to the guideline was needed.

For further details about the process and the possible update decisions that are available, see [ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual](#).

Information considered when developing the guidelines

Suspected cancer: recognition and referral

In relation to the rationale for only highlighting absent red reflex as a potential symptom of retinoblastoma in recommendation 1.12.2, the [full guideline](#) reports that 'no evidence was found pertaining to the positive predictive values of different symptoms of retinoblastoma in primary care.' The guideline development group (GDG) 'considered that a potential benefit of recommending which symptoms should prompt a suspected cancer pathway referral would be to identify those children with retinoblastoma more rapidly. However, the GDG recognised the importance of recommending the 'right' symptoms, in order to minimise the number of children without retinoblastoma who get inappropriately referred whilst maximising the number of children with retinoblastoma who get appropriately referred... the GDG also acknowledged that no evidence had been found on the positive predictive values of symptoms for retinoblastoma. Despite the lack of evidence, the GDG considered that it was still important to provide guidance on which symptoms should prompt referral for suspected retinoblastoma, since there was no test available in primary care. The GDG noted, based on their clinical experience, that an absent red reflex can be a symptom of retinoblastoma, which the GDG agreed was serious enough to warrant action... The GDG discussed whether other symptoms should prompt a suspected cancer pathway referral, but noted that the study included in the evidence by Dommett et al.

([2012](#), [2013a](#), [2013b](#)) had examined the positive predictive values for the symptoms recommended in previous guidance, and they were all very low. The GDG therefore decided not to make any further symptom-based recommendations.'

The reason for recommending an urgent (within 2 weeks) referral was that 'the GDG agreed that the most appropriate action would be urgent ophthalmological assessment (with an appointment within 2 weeks), rather than a suspected cancer pathway referral, as this assessment would reduce any delay associated with multiple, serial referrals. In addition, it would allow flexibility in where the referral was made (either to ophthalmology or paediatrics) depending on how services were set up locally.'

No new evidence on retinoblastoma was identified in the [2020 surveillance review of NICE's guideline on suspected cancer](#).

Suspected neurological conditions: recognition and referral

Recommendation 1.30.1 was based on the committee's knowledge and expertise with further validation by external experts through a targeted engagement exercise. The [rationale](#) provided is that 'New-onset squint with loss of red reflex in one or both eyes can indicate a retinoblastoma or other progressive pathology of the eye. Because of the risk of retinoblastoma spreading to the other eye, the committee agreed that referral should be immediate.'

The [full guideline](#) reports that 'Loss of red reflex can indicate a retinoblastoma or other progressive pathology of the globe.' Squint as a symptom was not prioritised for an evidence review for children because the GDG 'considered the referral decision to be non-contentious' and thought that 'an evidence review is unlikely to change this.' The guideline reports that 'because of the risk of retinoblastoma spreading to the other eye, the committee agreed that referral should be immediate (same day). Children presenting with the onset of squint and loss of red reflex in one or both eyes should be diagnosed, scanned and operated on as soon as possible to decrease the impact on the patient's vision. The committee recognised that the local service provision may vary, but ophthalmological services will be aware of the local pathway.'

Other relevant NICE guidance

[NICE's guideline on postnatal care](#) covers the routine postnatal care that women and their babies should receive in the first 8 weeks after the birth. This includes [recommendation](#)

1.3.3, which highlights that as part of Public Health England's newborn and infant physical examination (NIPE) screening programme, a complete examination of the baby should be carried out within 72 hours of the birth and at 6 to 8 weeks after the birth and this should include checking the baby's eyes for red reflex, opacities and colour of sclera. The primary purpose of the NIPE eye screening is to identify congenital cataracts, which 'cause a central shadow, completely obscure the red reflex or may make the reflex in one eye appear duller than the other. A severe cataract can make the pupil appear white when viewed with the naked eye'. If the assessment indicates an abnormal red reflex then the advice is to urgently refer the baby to an ophthalmologist within 2 weeks. The NIPE also says that 'parents should be advised to contact their midwife, GP or health visitor whenever they have any concerns about their baby's eyes or visual behaviour, including ... a white reflex, consistently seen on flash photography, asymmetry of the red reflex, consistently seen on flash photography'.

NICE guidelines do not make recommendations on the content of national screening programmes, as such the recommendations in the NICE guidelines on suspected neurological conditions and suspected cancer on referral if an absent red reflex, with or without new-onset squint, is identified in a child, is in relation to these symptoms presenting in a child at any time point outside of the NIPE screening programme.

Topic expert feedback

In this exceptional review we engaged with topic experts who were members of the GDG for the NICE guidelines on suspected cancer and suspected neurological conditions and topic experts who were members of the NICE Centre for Guidelines Expert Advisers Panel specialising in ophthalmology. Fourteen topic experts were contacted. Three of these topic experts responded: all professors, with 2 also consultants in ophthalmology. We also received 2 responses from specialists in ophthalmology with whom topic experts shared the online questionnaire. One described their specialty as ophthalmology and the other as a paediatric ophthalmologist and retinoblastoma surgeon.

Clinical reason for differences between recommendations

Topic experts were asked whether there is any clinical reason why urgent (within 2 weeks) referral is appropriate for children with an absent red reflex only, whereas immediate (within a few hours) referral is needed for children with an absent red reflex in the presence of new-onset squint.

Three of the topic experts responded that they did not think there was a clinical reason for the difference in referral times for an appointment for investigations to exclude neuroblastoma, for which absent red reflex is the key diagnostic finding and that this should be an 'urgent' rather than 'immediate' referral. However, 1 of these topic experts noted that bilateral disease is possible and that the combination of a squint as well as absent red reflex may suggest a larger retinoblastoma; and another topic expert highlighted that children with an acute squint with signs of neurological problems, might have raised intracranial pressure and an intracranial tumour, so should be seen immediately.

The 2 topic experts who responded that there were clinical reasons for the differences between the recommendations, also highlighted that an acute-onset squint concomitant with absent red reflex may indicate elevated intracranial pressure, which is a serious neurological condition requiring immediate referral; and that the clinical scenario may be a retinoblastoma (causing loss of red reflex) and a pineal tumour (pineoblastoma) causing mass effects and/or elevated intracranial pressure. The presence of a sudden onset squint was also described as possibly indicating direct involvement of a cranial nerve in a tumour.

Referral times

Topic experts were asked 'Currently, NHS practice following detection of an absent red reflex, regardless of other symptoms, is for a child to be urgently referred within 2 weeks to an ophthalmologist for further investigation. Do you agree that this should remain the case (as in recommendation 1.12.2 in NICE's guideline on suspected cancer)?'

Three topic experts agreed that referral within 2 weeks to an ophthalmologist after detection of an absent red reflex should remain, with 1 saying this is 'a reasonable time frame which is achievable in most UK settings and unlikely to affect outcomes adversely. Where adverse outcomes occur due to delay (and this happens often) it is because of misdiagnosis in primary care, often because the red reflex has not been examined, and the problem being inappropriately handled routinely like a non-paralytic squint'. One of these topic experts did note that a new-onset squint could indicate a serious neurological condition, so immediate referral is likely to be appropriate (as in recommendation 1.30.1 in NICE's guideline on suspected neurological conditions).

One topic expert thought referral within 24 hours for children with an absent red reflex (with or without new-onset squint) would be appropriate (quicker than the 2 weeks in NICE's guideline on suspected cancer, but longer than the 'few hours' referral time in

NICE's guideline on suspected neurological conditions). Another topic expert disagreed with the 2-week referral, saying that this should only be the case as part of the NIPE screening programme, whose primary aim is to detect congenital cataracts rather than a retinoblastoma (a rare condition); and that if the red reflex is found to be abnormal outside of the NIPE screening programme that 'it is very likely to be a new event and then immediate referral [within a few hours] would be appropriate'. This topic expert said they were surprised that the recommendation in NICE's guideline on suspected cancer is for urgent rather than very urgent (within 48 hours) or immediate referral and said that 'ophthalmologists would accommodate seeing a child with a new-onset absent red reflex much sooner than within 2 weeks, especially in a child with known cancer'.

Other comments about absent red reflex in children and referral times

Two topic experts questioned the rationale in NICE's guideline on suspected neurological conditions for immediate referral to stop the spread of retinoblastoma to the other eye. One topic expert said this was 'anatomically unlikely' and another said that this is not how retinoblastoma manifests in 2 eyes: bilateral retinoblastoma usually represents the occurrence, either simultaneously or sequentially, of a primary tumour in each eye in those with a genetic predisposition to retinoblastoma.

A topic expert reported on the results of an audit of referrals to their ophthalmology department for squint which found that GPs looked at red reflex in less than 1 in 10 cases and their opinion was that this led to eye tumours being diagnosed very late, resulting in loss of the eye and threat to systemic health and/or mortality (reference not provided/available).

Equalities

One topic expert referenced the findings from a cross-sectional study on the role of ethnicity and socioeconomic status in the presentation of retinoblastoma in patients with non-familial retinoblastoma diagnosed between 2005 and 2011 in the UK ([Bourkiza et al. 2020](#)). This study reported that neither social deprivation nor ethnicity was associated with (statistically significant) late presentation of retinoblastoma in the UK.

Another topic expert said that children from any ethnic group other than white and those from socio-economically disadvantaged groups are at much greater risk of blinding eye

disease in the UK ([Rahi and Cable 2003](#) and [Teoh et al. 2021](#)). However, in these 2 observational studies only 1% of the children identified with severe visual impairment or blindness had a retinoblastoma.

Overall decision

The recommendations on referral times for children with an absent red reflex in NICE's guidelines on suspected cancer and suspected neurological conditions were consensus recommendations, based on topic expertise. Topic experts involved in this surveillance review have confirmed that absent red reflex with a new-onset squint may represent a different clinical population from children presenting with an absent red reflex alone, with both populations requiring assessment for retinoblastoma, but the former possibly also having elevated intracranial pressure and/or a brain tumour, which would be considered as requiring immediate referral, as in recommendation 1.30.1 in NICE's guideline on suspected neurological conditions.

Three topic experts considered that the 2-week referral time was sufficient for seeing a child with absent red reflex only (recommendation 1.12.2 in NICE's guideline on suspected cancer). Two experts disagreed and preferred a faster referral. However, it appears that in practice, once an ophthalmologist receives the referral, they would see the child before 2 weeks.

Additional feedback on practice indicated that GPs may not be assessing red reflex in children with a squint, resulting in delayed diagnosis of retinoblastoma. Details of when the practice audit was undertaken are unknown, so the potential impact of the 2019 recommendations in NICE's guideline on suspected neurological conditions on GP practice cannot be inferred. NICE is unaware of uptake information on absent red reflex testing and referral by GPs.

In relation to inequalities, while it is of concern that children from any ethnic group other than white and those from socio-economically disadvantaged groups are at much greater risk of blinding eye disease in the UK, this is not specific to cases of retinoblastoma, and evidence indicates that neither social deprivation nor ethnicity are associated with late presentation of retinoblastoma in the UK.

In conclusion, as the difference in referral times may be due to different levels of urgency because of different clinical populations, the referral times in recommendation 1.12.2 in NICE's guideline on suspected cancer and recommendation 1.30.1 in NICE's guideline on

suspected neurological conditions will not be amended.

To support healthcare practitioners in assessing red reflex by considering whether or not there is a new-onset squint and knowing which referral time to request, we will:

- add cross-references from each recommendation to the other
- amend the rationale linked to recommendation 1.30.1 in NICE's guideline on suspected neurological conditions to remove reference to retinoblastoma spreading between eyes and clarify the potential neurological conditions associated with the combined symptoms of absent red reflex and new-onset squint: raised intracranial pressure and brain tumour.

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