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Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (CTYA)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected Children, Teenage and Young Adult (CTYA) cancer. Key themes have been determined from the literature. For each key theme e.g. individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NICE NG12 and SRG guidelines can be found for reference.

This document includes evidence on the following topics:

- Symptoms
- Investigations (accessed or conducted in primary care)
- Safety Netting
- Risk Stratification
- Emerging topics in this area

Background

Children, Teenage and Young Adult (CTYA) cancer is an umbrella term, encompassing multiple different types of cancers diagnosed in those aged 0-24. Typically, children's cancers are defined as cancers in those aged 0-14 years, and teenage/young adult cancers include those aged 15-24 years.

Around 130 children aged 0-14 years and 180 young people aged 15-24 years are diagnosed with cancer in Scotland every year. That is more than 2-3 per week, respectively (2018, 2019, 2021)[1].

Almost a third (31%) of children aged 0-14 years with cancer were diagnosed with leukaemia, and around a quarter (26%) were diagnosed with brain and CNS tumours (2012 – 2021). Survival for children with cancer is high, with 85% of children expected to live for five years or more after their diagnosis. Almost a quarter (23%) of 15–19-year-olds with cancer were diagnosed with lymphoma. Carcinomas and CNS tumours each made up more than almost a fifth (17%) of cases (2012-2021). A quarter (25%) of 20–24-year-olds with cancer were

[1] Children and young people with cancer in Scotland. Public Health Scotland. Accessed June 2024.

diagnosed with carcinomas, almost a fifth (18%) were lymphoma, and almost a fifth (16%) were melanoma (2012-2021). Cancer survival among young people is high, with 91% expected to live for five years or more after their diagnosis[1].

Symptoms and symptom onset can vary depending on cancer type, size of tumour, location, rate of growth, and age. There are several challenges to consider in the timely diagnosis of CTYA cancers. The biological nature of these cancers means they are often more aggressive than adult cancers, and may present very suddenly, representing a challenge for earlier diagnosis.

Patients often experience long patient intervals as a result of non-timely help seeking for symptoms, possibly due to lack of awareness of cancers in CTYA[2,3]. As CTYA cancer is rare, health professionals may not always initially suspect cancer and investigate other benign causes first, potentially leading to pathway delays. It has been estimated that a general practice will see a CTYA with cancer every 1.8 years and an individual GP may therefore see 1 every 5-10 years, or may never encounter CTYA cancer in their career[4].

Large variation is seen in diagnostic interval by cancer type, and it is common for patients to see a health professional 3 or more times prior to referral[5]. Evidence suggests that patients who are female, white, are diagnosed with lymphoma or bone tumours and those who are not seeking work or registered as long-term sick may be more likely to have multiple (3 or more) pre-referral consultations[2]. Continued review of the evidence underpinning referral guideline recommendations and their use, will help ensure people are referred along the most appropriate route at the right time.

Search Strategy

Search terms: PubMed search for combinations of the following terms: children/childhood, teenage, young adult, CTYA, cancer, neuroblastoma, retinoblastoma, wilms tumour, lymphoma, leukaemia, bone, gonadal, testicular, PPV, risk, prevalence, symptomatic, presentation, primary care, each symptom (e.g. petechiae, purpura, fatigue, persistent pallor, weight loss, persistent unexplained pain,

[2] Liu JF, Shanmugavadivel D, Ball-Gamble A, Stewart A, Walker D. Public awareness of childhood, teenager and young adult cancer signs and symptoms in Great Britain: a cross-sectional survey. Archives of Disease in Childhood [Internet]. 2023 Dec 1 [cited 2023 Dec 6];108(12):987–93. Available from: https://adc.bmj.com/content/108/12/987
[3] Hart RI, Cowie FJ, Jesudason AB, Lawton J. Adolescents and young adults' (AYA) views on their cancer knowledge prior to diagnosis: Findings from a qualitative study involving AYA receiving cancer care. Health Expectations. 2020 Dec 4;24(2):307–16.
[4] Children's Cancer and Leukaemia Group. Childhood Cancer: Care and Treatment. Information for GPs. Access here: Childhood_cancer_-_care_and_treatment_(GP)_2018.pdf (cclg.org.uk)
[5] Herbert, A. et al. Diagnostic timeliness in adolescents and young adults with cancer: a cross-sectional analysis of the BRIGHTLIGHT cohort. Lancet Child Adolesc Health 2, 180–190 (2018).

abdominal mass, distention, haematuria, bone pain, lymphadenopathy, headache, neurological symptom, mass, squint, pupillary reflex, fundal reflex), investigation (blood tests, imaging), recognition, referral, stage, routine, routes to diagnosis, safety netting, comorbidity

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review document.

Peer-reviewed literature

Topic: Symptoms
Summary: The evidence base largely supports symptoms included in the current guidelines. Evidence summarising PPV estimates for CTYA cancers post-2015 is very limited. A systematic review (paper 5) reported PPV estimates for symptoms associated with CTYA brain/CNS cancers, and found no symptoms exceed a 1% risk threshold. This broadly aligns with the evidence included in the NG12 evidence review document, which highlighted 2 papers investigating PPV data for CTYA cancers published pre-2015. The only symptom to exceed 1% risk was hepatosplenomegaly in the 0- 12 months before diagnosis for either neuroblastoma, retinoblastoma or Wilm's tumour in those aged 0-4 years (1.3%), or for those aged 0-14 years (2.1%)[6]. There are multiple studies reporting common symptoms in different cancer types. The 3 most common symptoms for CTYA cancers as a group, as summarised in paper 1 are lump or swelling (experienced by 52% of those diagnosed with CTYA cancers), extreme tiredness (38%) and unexplained pain (34%). Blood and brain cancers are more commonly researched compared to other CTYA cancers. In Paper 1, the most common symptom reported for leukaemia was extreme tiredness (73%). A systematic review investigating potential signs and symptoms of suspected leukaemia found that hepatomegaly and splenomegaly were also common (68% and 64% respectively). General symptoms such as fatigue, fever and weight loss were reported to be more frequent in patients with leukaemia or lymphoma, compared to solid tumours. Paper 4 found that headache is usually the most common symptom in those diagnosed with brain tumours, which supports the findings summarised in paper 1. This study also reported that symptoms vary by type of brain tumour and tumour grade. Headaches, nausea and vomiting and dizziness

[6] Dommett, R. M., Redaniel, M. T., Stevens, M. C. G., Hamilton, W., and Martin, R. M. Features of childhood cancer in primary care: A population-based nested case-control study. British Journal of Cancer 106[5], 982-987. 2012.

appeared to present more commonly in those with high-grade tumours (headaches: 75%; nausea and vomiting: 61%; dizziness: 27%). In contrast, the proportion of cases with convulsions/seizures was lowest in high-grade tumours (12%). A common sequence of symptoms was observed in most types of brain tumour: if headache was the first symptom, nausea/vomiting was the most frequent concurrent or following symptom, and focal neurological signs and symptoms the third.

The evidence below suggests that it is most common for CTYA cancers to present with multiple symptoms, but there is no evidence demonstrating increasing diagnostic accuracy for symptom combinations.

There is less high-quality, recent evidence for cancer types in CTYA that are much less common e.g. bladder, retinoblastoma and sarcomas. Compared to cancer in adults, the CTYA evidence base is often from an international perspective, likely due to the relatively small numbers of cases.

A Delphi Consensus study (Footnote 9) of 133 health professionals developed sixty-four new evidence-based statements on best practice, assessment, imaging and referral of children and young people with signs and symptoms of suspected cancer. Some of the key best practice statements about bone and abdominal symptoms are:

- Be aware that bone tumours can present with systemic symptoms, such as fever, malaise and weight loss.
- Be aware that bone and abdominal tumours causing spinal cord compression can affect bladder and bowel function, and cause neurological symptoms.
- Have a high level of concern for a CTYA who is normally highly active but is no longer able to play sport due to presenting symptom
- Be aware that weight loss can be a sign of an abdominal tumour

Paper number	Study	Cancer site	Summary	Notes
1	Koo MM, Lyratzopoulos G, Herbert A, Abel GA, Taylor RM, Barber JA, et al. Association of Self-reported Presenting Symptoms With Timeliness of	All	This study aimed to examine (1) common presenting symptoms in adolescents and young adults aged 12 to 24 years who subsequently received a diagnosis of cancer and (2) potential variation in time to help-seeking by presenting symptom. Commonality of symptoms (number, %, 95% Cis): • Lump or swelling: 419 (52) [49-56] • Extreme tiredness: 308 (38) [35-42]	Multicentre study, cross-sectional analysis of the BRIGHTLIGHT cohort study in England Data collected between 2018-2019

	Help-Seeking Among Adolescents and Young Adults With Cancer in the BRIGHTLIGHT Study. JAMA Network Open. 2020 Sep 3;3(9):e2015437.		• Unexplained pain: 281 (34) [32-38] • Night sweats: 192 (24) [21-27] • Lymphadenopathy: 191 (24) [21-27] • Weight loss: 190 (24) [21-27] • Headaches: 127 (16) [13-19] • Dizziness: 126 (16) [13-18] • Rash or itching: 94 (12) [10-14] • Limping or mobility problems: 77 (10) [8-12] • Bruising or bleeding: 73 (9) [7-11] • Other symptoms: 69 (9) [7-11] • Menstrual changes: 56 (7) [5-9] • Recurrent infections: 47 (6) [4-8] • Mole changes: 40 (5) [4-7] • Loss of vision: 27 (3) [2-5] • Fits or seizures: 17 (2) [1-3] 69% of the sample reported experiencing multiple symptoms. Patients with leukaemia (86%) and lymphoma (77%) were most likely to report multiple symptoms, whereas those with melanoma were least likely to report multiple symptoms (31%). **Cancer Site–Specific Symptom Signatures** (includes 10 most common symptoms per site) **Lymphoma (n=260)** • Lump/swelling: 157 (60%) • Lymphadenopathy: 144 (55%) • Extreme tiredness: 125 (48%) • Night sweats: 113 (43%) • Weight loss: 94 (36%) • Unexplained pain: 68 (26%)	Semi-structured interviews linked to cancer registry data N=803 Aged 12-24 years **Limitations:** there is risk of recall bias as this study uses self-reported information on symptoms and intervals to help-seeking. Additionally, this will exclude patients with poor prognosis who may die soon after their diagnosis, leading to survival bias.

			• Rash/itching: 61 (23%) • Dizziness: 41 (16%) • Headaches: 34 (13%) • Limping/mobility problems: 21 (8%) **Germ cell cancers (testicular, ovarian or 'other': n=155)** • Lump/swelling: 114 (74%) • Unexplained pain: 65 (42%) • Extreme tiredness: 33 (21%) • Weight loss: 16 (10%) • Night sweats: 14 (9%) • Dizziness: 14 (9%) • Headaches: 14 (9%) • Lymphadenopathy: 11 (7%) • Other symptoms: 9 (6%) • Menstrual changes: 9 (6%) **Leukaemia (n=102)** • Extreme tiredness: 74 (73%) • Headaches: 41 (40%) • Bruising/bleeding: 40 (39%) • Weight loss: 36 (35%) • Dizziness: 35 (34%) • Unexplained pain: 33 (32%) • Night sweats: 31 (30%) • Other symptoms: 16 (16%) • Lymphadenopathy: 15 (15%) • Lump/swelling: 13 (13%) **Carcinomas (n=94)** • Lump/swelling: 51 (54%) • Unexplained pain: 38 (40%) • Extreme tiredness: 36 (38%)	

			• Dizziness: 14 (15%) • Menstrual changes: 14 (15%) • Night sweats: 13 (14%) • Bruising/bleeding: 13 (14%) • Weight loss: 13 (14%) • Lymphadenopathy: 12 (13%) • Other symptoms: 11 (12%) **Bone (n=78)** • Lump/swelling: 50 (64%) • Unexplained pain: 47 (60%) • Limping/mobility problems: 33 (42%) • Weight loss: 14 (18%) • Extreme tiredness: 10 (13%) • Night sweats: 8 (10%) • Other symptoms: 6 (8%) • Menstrual changes: 4 (5%) • Headaches: 3 (4%) • Lymphadenopathy: 3 (4%) **Soft tissue sarcomas (n=44)** • Lump/swelling: 29 (66%) • Unexplained pain: 15 (34%) • Extreme tiredness: 10 (23%) • Weight loss: 7 (16%) • Other symptoms: 7 (16%) • Night sweats: 5 (11%) • Dizziness: 4 (9%) • Headaches: 4 (9%) • Lymphadenopathy: 3 (7%) • Limping/mobility problems: 3 (7%) **CNS (n=31)**	

			• Headaches: 22 (71%) • Extreme tiredness: 13 (42%) • Dizziness: 11 (35%) • Fits/seizures: 10 (32%) • Loss of vision: 9 (29%) • Unexplained pain: 7 (23%) • Weight loss: 7 (23%) • Other symptoms: 4 (13%) • Night sweats: 4 (13%) • Limping/mobility problems: 2 (6%) **Melanoma (n=29)** • Mole changes: 24 (83%) • Rash/itching: 7 (24%) • Lump/swelling: 3 (10%) • Night sweats: 2 (7%) • Lymphadenopathy: 2 (7%) • Recurrent infections: 1 (3%) • Extreme tiredness: 1 (3%) • Weight loss: 1 (3%) • Limping/mobility problems: 1 (3%) • Unexplained pain: 1 (3%)	
2	Clarke RT, Van den Bruel A, Bankhead C, Mitchell CD, Phillips B, Thompson MJ. Clinical presentation of childhood leukaemia: a systematic review	Leukaemia	This study aimed to systematically review all existing data on clinical presentation and estimated the frequency of signs and symptoms presenting at or prior to diagnosis. For the meta-analysis, the authors aggregated 15 features into 6 overarching categories: • petechiae/purpura (including 'petechiae', 'purpura' and 'petechiae/purpura')	Systematic review and meta-analysis. Papers published up to 2014 included. Age range: 0-18 years

	and meta-analysis. Archives of Disease in Childhood. 2016 Sep 19;101(10):894–901.		• mucosal bleeding (including 'mucosal bleeding' and 'bleeding gums') • anorexia/weight loss (including 'anorexia', 'weight loss' and 'anorexia/weight loss') • weakness/fatigue (including 'weakness', 'fatigue', 'weakness/fatigue') • malaise/fatigue (including 'malaise' and 'malaise/fatigue') • infections (including 'infection' and 'recurrent infections'). Signs and symptoms present in more than 1/3 of leukaemia patients: • Hepatomegaly: 64% • Splenomegaly: 61% • Pallor: 54% • Fever: 53% • Bruising: 52% • Infections: 49% • Fatigue: 46% • Limb pain: 43% • Hepatosplenomegaly: 42% • Bruising/petechiae: 42% • Lymphadenopathy: 41% • Bleeding tendency: 38% • Rash: 35% There were 36 features that were present in ≥10% of children. These were grouped into seven distinct clinical categories: infiltrative, haemorrhagic, infective, systemic, musculoskeletal, gastrointestinal and cutaneous.	N=33 studies conducted in 21 countries. Describes presenting symptoms and signs in a total of 3084 children. **Limitations:** studies provided data on cases only, and not on controls, so the authors were unable to determine diagnostic accuracy of clinical features

			The most common infiltrative symptoms were hepatomegaly (64%) and splenomegaly (61%). Bruising, the most common haemorrhagic symptom, occurred in 52% of children. Fever (53%) was the most common infective symptom, and the most common musculoskeletal features were limb pain (43%) and bone pain (26%). Systemic features such as pallor (54%) and fatigue (46%) were also common. Finally, the most common gastrointestinal feature, anorexia/weight loss (29%), was present in almost a third of children. Features of acute illness, e.g. fever, were more common in acute leukaemia (62%, 95% CI 51-73) than chronic leukaemia (31%, 95% CI 13-49), whereas certain more progressive features, e.g. splenomegaly, were more prominent in chronic leukaemia (77%, 95% CI 62-92) than acute (56%, 95% CI 40-73).	
3	Lilja-Fischer JK, Schrøder H, Nielsen VE. Pediatric malignancies presenting in the head and neck. International Journal of Pediatric Otorhinolaryngology. 2019 Mar;118:36–41.	Leukaemia/ lymphoma	This study aimed to estimate the proportion of childhood cancer cases with a primary head and neck presentation, and to describe symptoms, physical findings, diagnostic interval and tentative diagnoses. N=85 childhood cancer patients presented with primary head and neck presentation (15% of the total population of patients with childhood cancer). The most frequent diagnoses were acute leukaemia (33%) or lymphoma (29%) The most common symptoms reported in the initial medical records were a **tumour or swelling**, as noted by the patient or others, reported in 62 of 85 patients (73%, 95% CI: 62-82%). Other	Retrospective cohort study, using data from Danish Childhood Cancer Registry between 2003-2013. Age range: <15 years N=584 childhood cancer diagnoses **Limitations:** this study was conducted in Denmark, which may limit the

			common symptoms were **fatigue** in 35% (CI: 25-46%), **fever** in 27% (CI: 18-38%) and **pain** in 22% (CI: 14-33%). Across all cancer types, tumour or swelling was a prominent symptom, whereas general symptoms such as fatigue, fever and weight loss were more frequent in patients with leukaemia or lymphoma. Patients had a mean of 2.8 symptoms recorded (95% CI: 2.5-3.2). Patients with leukaemia had significantly more symptoms than patients with lymphoma or solid tumours Extra-cervical lymphadenopathy, hepatosplenomegaly, pallor or petechiae was only common among patients with leukaemia, seen in 25-46% of these patients. Physical findings among patients with solid tumours were dependent on anatomic location of the tumour. The most frequent locations of solid tumours were the neck, orbit and nasopharynx.	applicability to UK health setting
4	Zumel-Marne A, Kundi M, Castaño-Vinyals G, Alguacil J, Petridou ET, Georgakis MK, et al. Clinical presentation of young people (10–24 years old) with brain tumors: results from the international	Brain	This study used information from a clinical questionnaire to explore clinical characteristics of brain tumours in children aged 10-24. The majority of patients were diagnosed with neuroepithelial tumours (76%). Gliomas represented 62% of all tumours; other neuroepithelial tumours were a variety of different cancer types, such as ganglioglioma NOS (n=55), dysembryoplastic neuroepithelial tumours (n=23), central neurocytomas (n=18), among other rare tumours.	Multinational case–control study (MOBI-Kids) aiming to estimate risk of brain tumours in relation to electromagnetic fields exposure from use of mobile communication device between 2010-2016.

	MOBI-Kids study. Journal of Neuro-Oncology. 2020 Mar 3;147(2):427–40.		Among non-neuroepithelial tumours, embryonal tumours were the most frequent (14% of all tumours), followed by meningioma (5%). Overall, people diagnosed symptomatically had a median of 3 symptoms recorded; the median was lower (2) in cases in those 15–24 years old compared to younger patients ($p<0.01$). Females reported more symptoms (median: n=3) than males (median: n=2). **Non-neuroepithelial tumours** People with embryonal tumours had more symptoms (median=4), than other types of tumour (median=2–3). The number of symptoms tended to be higher in higher grade tumours. For those with at least one symptom, the most frequently reported were **headaches** (n=436; 60% of cases with symptom information), focal neurological signs and symptoms (n=287; 40%), nausea/vomiting (n=277; 38%) and visual signs and symptoms (n=217; 30%) **Neuroepithelial tumours** The majority of people diagnosed with glioma reported **headaches** (64% in high-grade, 59% in low-grade tumours), whereas the most frequent symptoms reported for other neuroepithelial tumours were **convulsions/seizures** (53%) and headaches (46%). The proportion of people presenting with headaches, nausea and vomiting and dizziness varied by grade, being highest for grade 4 tumours (headaches: 75%; nausea and vomiting: 61%; dizziness:	Symptoms were reported by clinicians and retrieved from medical notes n=722 Ages: 10-24 years Countries included: Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, New Zealand, Spain, Netherlands, Japan and Korea. **Limitations:** exclusion criteria used in the MOBI-Kids study excluded pituitary tumours, which are quite frequent in this age range

			27%). In contrast, the proportion with convulsions/seizures was lowest in high-grade tumours (12%). A common sequence of symptoms was observed in most cancer types: if headache was the first symptom, nausea/vomiting was the most frequent concurrent or following symptom, and focal neurological signs and symptoms the third.	
5	Schmidt-Hansen M, Berendse S, Hamilton W. Symptomatic diagnosis of cancer of the brain and central nervous system in primary care: a systematic review. Family Practice. 2015 Oct 14;32(6):618–23.	Brain/CNS	This study aimed to quantify the risk of brain/CNS cancer in symptomatic patients presenting in primary care. The PPV of the individual symptoms studied was very low. The highest was 0.02% for seizure for those aged 0-14 and 15-24 years. All symptom combinations included had a PPV of <1%.	Systematic review Papers included from 1980-2014 N=6 papers included, n=159,938 patients **Limitations:** most studies included used case–control methods, which can lead to bias from patient selection.
6	Saltsman JA, Malek MM, Reuter VE, Hammond WJ, Danzer E, Herr HW, et al. Urothelial neoplasms in pediatric and young adult patients: A large single-center series. Journal of Pediatric Surgery. 2018 Feb;53(2):306–9.	Bladder	This study aimed to review bladder urothelial neoplasms in paediatric and young adult patients, summarising presentation, treatment, and outcomes. Histologic diagnoses were invasive urothelial carcinoma (n=3), non-invasive urothelial carcinoma (n=24; 22 low grade, 2 high grade), PUNLMP (n=6), and urothelial papilloma (n=1). The most common symptom at presentation was haematuria, present in 76% (n=26). Abdominal/pelvic pain was present in 26% (n=9).	Single-centre evaluation (USA) using surgical pathology records of cases of urothelial neoplasms among patients ≤25 years of age treated between 1997-2016 N=34 **Limitations:** this study is based in USA and included

				a very small sample size, which may limit applicability to UK setting
7	Global Retinoblastoma Study Group, Fabian ID, Abdallah E, Abdullahi SU, Abdulqader RA, Adamou Boubacar S, et al. Global Retinoblastoma Presentation and Analysis by National Income Level. JAMA oncology [Internet]. 2020 May 1;6(5):685–95.	Retinoblastoma	This study aimed to report stage at diagnosis in patients diagnosed with retinoblastoma across the world during a single year, to investigate associations between clinical variables and national income level, and to investigate risk factors for advanced disease at diagnosis. The most common stage at diagnosis was stage 3 (47%), with small proportions of metastases or lymph node involvement (7% and 23%, respectively). The most common first symptom of disease (as recognised by parents) was leukocoria (abnormal pupillary reflex)(n = 2638 (62.8%)), followed by strabismus (n = 429 (10.2%)), with a further 162 (3.9%) patients having a combination of leukocoria and strabismus. Proptosis was reported in 309 (7.4%) patients. At least 1 symptom of advanced disease (proptosis, swollen eyelids, red eye) was reported in 487 (11.7%) patients.	Cross-sectional analysis using data from participating treatment centres in 2017 N= 4351 new patients from 153 countries **Limitations:** a large proportion of participants included were from LMICs, which may limit applicability to UK context
8	Kiernan M, Fabian ID, Smith V, Sagoo MS, Reddy MA. Strabismus as a Presenting Sign in Retinoblastoma. Journal of Pediatric Ophthalmology &	Retinoblastoma	This study aimed to report the presenting signs of retinoblastoma in a cohort of patients who underwent orthoptic assessment at presentation. The most common examination findings were leukocoria only (n= 73, 56%), followed by leukocoria with strabismus (n = 23, 18%), and strabismus (n = 17, 13%).	Retrospective medical chart review at a single centre in England, referred between 2009 and 2015 N=131

	Strabismus. 2021 Sep;58(5):324–30.		Eleven (8%) patients presented with periocular inflammation. The remaining 6 (5%) patients presented with 'other' signs and symptoms; iris colour change, proptosis, floaters, nystagmus, and an incidental radiological finding of retinoblastoma.	**Limitations:** this is a small sample and data was obtained from medical records which may limit accuracy of findings
9	Shanmugavadivel, D & Liu, Jo-Fen & Stewart, A & Gamble, A & Walker, David. (2020). What are the signs and symptoms of bone tumours in childhood? are the great british public aware of them?. Archives of Disease in Childhood. 105. A61.2-A62. 10.1136/archdischild-2020-rcpch.146.	Bone tumours	This study aimed to (1) identify the core signs/symptoms of bone tumours in childhood and (2) understand public awareness of these symptoms. 29 symptoms/signs were reported in the study but only those that occurred in 2% or more of patients are reported: Pain (76%), swelling (21%), fever (4%), history of trauma (3%), functional limitation (3%), palpable mass (3%), pain and swelling (2%), volume increase (2%), limp (2%) and pathological fracture (2%). Public awareness reported in the survey of the top 4 presenting symptoms of bone tumours were low (range: 14-23%).	Conference abstract only Systematic review and survey Papers included from 2005-2015 N=11 studies included, including 1,246 children N=1,000 survey participants **Limitation:** as this is a conference abstract, the quality and type of the studies included in the systematic review cannot be ascertained. It is unclear whether the reported symptoms are from medical records, or reported by health professionals/patients

Topic: Investigation findings
Summary:

There is very limited evidence investigating primary care investigations for CTYA cancers.

Cervical cancer in young women represents a diagnostic challenge because gynaecological symptoms are common, but this type of cancer is incredibly rare in CTYA. There is limited evidence determining the accuracy of visualisation of the cervix in primary care, but one study reported that findings from visualisation were not commonly documented in medical notes, and rarely leads to onward referral or investigation. Paper 11 investigates the use of cytology as a diagnostic aid and estimates performance characteristics for cytology performed in a symptomatic cohort (sensitivity: 96.2% and specificity: 84.6% for very high-grade cell changes). Further research is needed to optimise investigation of suspected cervical cancer/cervical abnormality in primary care for young women.

A Delphi Consensus study (Footnote 9) of 133 health professionals developed sixty-four new evidence-based statements on best practice, assessment, imaging and referral of children and young people with signs and symptoms of suspected cancer. Some of the key best practice statements about investigations are:

- Examination using paediatric Gait, Arms, Legs and Spine assessment (pGALS) is recommended for those with signs and symptoms of suspected bone tumours
- Be aware that x-ray is not always the most suitable imaging modality for persistent bony back pain. Discuss with a paediatric radiologist.

Paper number	Study	Cancer	Summary	Notes
10	Lim, A.W.W., Hamilton, W., Hollingworth, A., Stapley, S. and Sasieni, P. (2016). Performance characteristics of visualising the cervix in symptomatic young females: a review of primary care records in females with and without cervical cancer. British Journal of General	Cervical	This study aimed to assess visualisation of the cervix in primary care in young females with gynaecological symptoms. In primary care records, 52%* (56 of 107) of women with cervical cancer had gynaecological symptoms recorded in the year before diagnosis. Of these, 39% (22 of 56) had a documented cervical examination at the time of symptomatic presentation. This resulted in specialist referral for a clinically suspicious cervix in 4 females (18%, 95% CI: 5%-40%). 2	Mixed-method study using multiple datasets: nationwide interview-based study of young females aged 18–29 years diagnosed with cervical cancer in England between 2010-2012 Also utilised GP primary care record data, cervical screening history (from the national screening database Exeter Call/Recall System), CPRD data from 1990-2010

	Practice, 66(644), pp.e189–e192. doi:https://doi.org/10.3399/bjgp16x683833.		other women whose cervix was not documented as 'suspicious' were also referred for urgent assessment: their findings on examination were recorded as 'normal' or 'red and friable'. Visualisation identified 1 out of 8 stage 1A, and 3 out of 14 stage 1B or worse cervical cancers. *this percentage was reportedly much higher (89%) in interviews. In the CPRD dataset, between 0.6% and 1.6% of females aged 20–29 years who presented with a gynaecological symptom had documented evidence of cervical examination within 14 days. None resulted in colposcopy referral.	N= 45,484 consultation data available **Limitations:** the study sample has a small number of cervical cancer cases. Primary care records tend to underreport unexplained symptoms, and CPRD data only includes coded symptoms, so this may be an underestimation of cervical cancer symptoms and investigations in primary care.
11	Lim, A.W., Landy, R., Castanon, A., Hollingworth, A., Hamilton, W., Dudding, N. and Sasieni, P. (2016). Cytology in the diagnosis of cervical cancer in symptomatic young women: a retrospective review. British Journal of General Practice, 66(653), pp.e871–e879. doi:https://doi.org/10.3399/bjgp16x687937.	Cervical	Cytology has a well-established role in cervical cancer prevention but its role in diagnosis is less established. This study explored the potential of cytology as a diagnostic aid for cervical cancer in young women. 22 of 107 women with primary care record data had a symptomatic cytology test. Symptoms reported ahead of tests were: postcoital bleeding (n=17), intermenstrual bleeding (n=6), vaginal discharge (n=7), heavy or frequent periods (n=4), and dyspareunia (n=1). **Sensitivity determined using primary care records:**	Data utilised with four datasets: primary care records, national audit of cervical cancer, whole population cytology from national screening and Clinical Practice Research Datalink (CPRD) Data included from 2007-2014 N=107 from primary care data with symptomatic cytology test N=72 from audit data diagnosed with cervical cancer

			Sensitivity of high-grade cytology (borderline high risk, or moderate dyskaryosis, or worse): **90.9%** (95% CI = 70.8-98.8) Sensitivity of very high grade (severe or worse) cytology: **81.8%** (95% CI= 59.7-94.8). None of these 22 women had negative cytology. **Sensitivity determined using national audit data:** From the national audit, 36% (26/72) had a cytology test before their first screening invitation (this was presumed by the authors to be in response to symptoms, but this cannot be ascertained from the study). The sensitivity of cytology for high grade was **96.2%** (95% CI = 80-99%), and **84.6%** (95% CI = 65-96%) for very high grade. None of these women had negative cytology. The sensitivity in symptomatic women calculated from national audit data was similar to that in all women (screened and symptomatic). PPVs were calculated in this study using national audit data and CPRD data, but they included both those diagnosed via symptomatic and screening routes (mostly screening): • High-grade cytology for invasive cervical cancer was 1.01% (95% CI =0.8-1.2). • High grade (aged 25–29 years): 1.74% (95% CI = 1.6 to 1.9). • Very high grade (aged 20-24) was 2.0% (95% CI = 1.6 to 1.9)	N= 1842 cytology tests in CPRD Age: 20-29 years **Limitations:** Whole-population cytology from the national screening database was not recent (2007 to 2010), and the sample includes relatively small numbers of symptomatic presentations

			• Very high grade (aged 25-29) was 3.15% (95% CI = 2.9 to 3.4)	

Topic: Safety Netting
Summary: In paper 12, 86% of CTYA cancers diagnosed presented to primary care first, demonstrating the importance of accurate referral guidelines and timely referral. Patient and primary care intervals vary by cancer type. For lymphoma, 60% of patients who had consulted with primary care had done so ≥5 times before the start of treatment. This data is from 2014-2016 and includes a relatively small sample, which may affect the reliability of these findings. Paper 13 compared outcomes for those with Wilms tumour in both Germany and UK. The study reported slightly higher survival in Germany. The authors attributed this to a greater proportion of incidental findings, which are associated with earlier stage at diagnosis. A Delphi Consensus study (Footnote 9) of 133 health professionals developed sixty-four new evidence-based statements on best practice, assessment, imaging and referral of children and young people with signs and symptoms of suspected cancer. Some key safety netting statements highlighted in this review were: • Be aware that low parental education level, social deprivation, and lack of familiarity with the UK health system may be associated with diagnostic delay. Consider an MDT approach for these families e.g. health visit liaison and provide clear written safety netting for when to seek further medical advice. • Be aware that an initial normal x-ray does not exclude a bone tumour. If symptoms or clinical suspicion persists, a referral to secondary care is warranted. • Be aware that children aged <4 years, or those with communication difficulties are often unable to describe pain. Their behaviour e.g. withdrawal or reluctance to weight bear may indicate bone pain. • Be aware that perceived diagnostic delay has been associated with failure to perform an abdominal examination in a child who is distressed/crying. • Be aware that perceived delayed diagnosis has been associated with common misattributions, such as: attributing a red warm swelling to infection despite no improvement with antibiotics, attributing abdominal pain and/or mass to constipation despite no improvement with laxatives and associating persistent haematuria to a UTI despite no response to antibiotics.

Paper number	Study	Cancer	Summary	Notes
12	Dommett RM, Pring H, Cargill J, Beynon P, Cameron A, Cox R, et al. Achieving a timely diagnosis for teenagers and young adults with cancer: the ACE "too young to get cancer?" study. BMC Cancer. 2019 Jun 24;19(1).	All	This study aimed to understand referral pathways in a cohort of newly diagnosed patients referred to a regional care network for TYA cancer in the Southwest of England. Diagnoses were as follows (n (%)): • Lymphoma 29 (28%) • Carcinoma 21 (20%) • Leukaemia 18 (17%) • Germ cell tumours 10 (10%) • Brain/CNS tumours 7 (7%) • Bone tumour 7 (7%) • Soft tissue sarcoma 6 (6%) • Melanoma 5 (5%) • 'Other' 1 (Wilms' tumour). First presentation was to primary care for 86% of participants, and 93% consulted in primary care before diagnosis. Patient interval (time from first symptom to first presentation) was longest for lymphoma, carcinoma (type not specified) and bone tumours (median: 9, 12, 20 days respectively). Overall, the primary care interval was short (median 3, range 0–537 days) compared to the secondary care interval (median 29, range 0–195 days) and longest for	Service evaluation project initiated within the ACE (Accelerate, Coordinate, Evaluate) programme established in England in 2014-2016 n=104 Aged 15-18 years **Limitations:** this study includes a small sample, which may affect reliability of the findings and limit applicability of the results to a wider population

			lymphoma, carcinoma, brain/CNS (median: 10, 15, 16 days respectively). The frequency of primary care consultation varied by cancer site. For example, 15/25 (60%) patients with lymphoma who had consulted primary care had done so ≥5 times before start of treatment. Routes to Diagnosis (RTD): • 45% via urgent cancer pathway • 38% as emergency presentation (any) RTD varied by diagnostic group: • All malignant melanoma patients and over half of lymphoma patients were referred and diagnosed via urgent cancer pathway, compared with only 1/7 bone sarcoma and 0/7 of the brain/CNS tumour patients. • Of the 40 (38%) patients who presented as emergencies, 16 had leukaemia (89% of all leukaemia patients). • Other than leukaemia, those with brain/CNS tumours (4/7, 57%), carcinoma (6/21, 29%) and lymphoma (6/29, 21%) were the largest contributors to emergency presentations • Overall, 37% of all patients diagnosed via an emergency route were considered to have had opportunities for an earlier referral.	

13	Pritchard-Jones K, Graf N, van Tinteren H, Craft A. Evidence for a delay in diagnosis of Wilms' tumour in the UK compared with Germany: implications for primary care for children. Archives of Disease in Childhood [Internet]. 2016 Mar 6 [cited 2019 Sep 26];101(5):417–20.	Wilms Tumour	This review aimed to compare pathways to diagnosis and outcomes for people diagnosed with Wilms' tumours in Germany and the UK. • Stage at diagnosis and tumour volume at diagnosis was higher in the UK compared with Germany • Event-free survival (EFS) and overall survival was around 3% lower in the UK More patients were diagnosed incidentally in Germany, compared to the UK. The authors suggest this may be due to fewer routine examinations or examinations based on minor symptoms in the UK.	Review of clinical trial data (Germany and UK taking part in same clinical trial, enabling comparison), and both national groups have additional data on the route to diagnosis N=1,567 participants included **Limitations**: health systems and populations differ between Germany and England, which can make comparisons challenging

Topic: Risk Factors				
Summary: Lifestyle risk factors have less impact on cancer risk in childhood, because of less exposure to risk factors compared to adults. Overall, evidence on risk factors for childhood cancer is limited, mainly because of the relative rarity and diversity of this group of cancers[7]. The papers summarised below found that overall increased birthweight is associated with increased risk of childhood cancer, with some variation between cancer type. There is some evidence focusing on maternal substance use and risk of childhood cancer, suggesting that this does increase risk of childhood cancers overall with some variation by form of substance abuse and type of cancer.				
Paper number	**Study**	**Cancer**	**Summary**	**Notes**

[7] Cancer Research UK. Children's cancer statistics [Internet]. Cancer Research UK. 2015. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers#heading-Three

14	O'Neill KA, Murphy MFG, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. International journal of epidemiology. 2015 Jan 25;44(1):153–68.	All	This study aimed to analyse the relationship between birthweight and the entire spectrum of childhood tumours. In both datasets, increasing birthweight was associated with an increased risk of any childhood cancer, with each 0.5 kg increase in birthweight elevating risk by 6%. Risk differed by tumour sub-type and age.	Retrospective analysis of two large independent datasets: 1. Data for 16,554 cases and 53,716 controls were obtained by linkage of birth to cancer registration records across five US states 2. 23,772 cases and 33,206 controls were obtained from the UK National Registry of Childhood Tumours. **Limitations:** UK data was not adjusted for the following factors: lack of information on gestational age, maternal age, plurality, birth order and maternal race/ethnicity for the UK data which may influence the results
15	Paltiel O, Tikellis G, Linet M, Golding J, Lemeshow S, Phillips G, et al. Birthweight and Childhood Cancer: Preliminary Findings from the International Childhood Cancer Cohort Consortium (I4C). Paediatric and Perinatal Epidemiology [Internet]. 2015 Jul 1 [cited 2022 Dec 6];29(4):335–45.	All	This study aimed to investigate the association between birthweight and childhood cancer, exploring the potential modifying roles of age at diagnosis and maternal anthropometrics. When birthweight was considered as a continuous variable, a significant increased risk of 26% for every kilogram increment in birthweight was observed for all cancers, after adjustment for gestational age (GA) and sex [HR 1.26 (95% CI 1.02, 1.54), P = 0.031].	Prospective cohort study using 6 databases: the Avon Longitudinal Study of Parents and Children (UK), the Collaborative Perinatal Project (USA), the Danish National Birth Cohort (Denmark), the Jerusalem Perinatal Study (Israel), the Norwegian Mother and Child Cohort Study (Norway), and the Tasmanian Infant Health Survey (Australia), from 1959-2007 Included all those diagnosed with cancer aged <15 years

			The findings appear to be driven significantly by leukaemia. There was a 42% increase in risk observed for leukaemia, adjusting for GA and child's sex, with borderline statistical significance. Hazard ratios were elevated for children born with birthweight ≥4.0 kg, compared with those with lower birthweight for all cancer outcomes, although the findings were not statistically significant. In models adjusted for GA and sex, a significant association between birthweight, using all metrics, was observed for cancers occurring at or after age 3 years, but this was not significant for children younger than 3.	N= 112,781 **Limitations:** Pooling data from different cohorts may be problematic due to differences in populations.
16	Auger N, Goudie C, Low N, Healy-Profitós J, Lo E, Luu TM. Maternal use of illicit drugs, tobacco or alcohol and the risk of childhood cancer before 6 years of age. Drug and Alcohol Dependence. 2019 Jul;200:133–8.	All	This study aimed to investigate the association between maternal substance use and risk of childhood cancer within 0–5 years of age in a large cohort of newborns. The adjusted hazard ratio for childhood cancer overall was minimally elevated for any maternal substance use investigated in this study. Substance use was associated with 1.09 times the risk of any cancer (95% CI 0.86–1.38). This varied for different forms of substance abuse, e.g., illicit drug use was associated with 1.23 times the risk of hematopoietic cancer (95% CI 0.65–2.34), and	Observational cohort study using Canadian data Children aged 0-5 years included N=3,511,487 person-years of follow-up in the study and 925 incident cases of cancer (26.3 per 100,000 person-years). **Limitations:** the study could not fully identify all women with mild or undocumented substance use, which may have impacted the findings

			tobacco use was associated with 1.17 times the risk (95% CI 0.74–1.86). Maternal substance use appeared to be more strongly associated with hematopoietic cancer than solid tumours.	

Emerging Topics:

Medication use

There is emerging evidence investigating how exposure to certain medications during pregnancy could impact risk of childhood cancer[8], but this requires much further research.

ChildCancerSmart

ChildCancerSmart is a project aiming to reduce time taken to diagnosis in CTYA cancers. It will measure and understand the time it takes to diagnose CTYA with cancer across the UK and start to address delays by developing high-quality guidance on cancers in CTYA and produce awareness tools for a national awareness campaign to promote earlier diagnosis. It will involve a systematic review of the literature on signs, symptoms and diagnosis of childhood cancers and the results will be used to inform and develop referral guidelines for GPs and other HCPs. It will also involve a series of e-learning modules for HCPs based on the referral guidelines, a website with signs and symptoms materials, along with a public awareness campaign, will be developed for the public. The Childhood Cancer Diagnosis study is a UK observational study (part of ChildCancerSmart project) that is aiming to understand the current pathway of childhood cancer referrals and diagnoses, and quantify diagnostic intervals in the UK. The primary outcome measure is total diagnostic interval, with secondary measures of primary care interval and diagnostic interval.

The BENCHISTA project

[8] Momen NC, Olsen J, Gissler M, Kieler H, Haglund B, Li J. Exposure to systemic antibacterial medications during pregnancy and risk of childhood cancer. Pharmacoepidemiology and Drug Safety. 2015 May 29;24(8):821–9.

The International Benchmarking of Childhood Cancer Survival by Stage (BENCHISTA) Project will provide the first ever standardised data on CTYA tumour stage and survival to allow meaningful comparisons across Europe and other Westernised countries (Australia, Brazil, Japan and Canada). The project aims to improve understanding of the reasons for variation in childhood cancer survival between countries and to highlight areas to be targeted for improvement. It is expected that the project will reveal variation in stage at diagnosis and survival by stage between some countries, which would suggest improvement initiatives should include efforts to achieve earlier diagnosis.

Artificial intelligence

Because of the difficulty in diagnosing cancers in CTYA, innovations in diagnostic technologies need to be developed and assessed. It's much harder to apply AI to CTYA cancers than adult cancers because AI models need large data sets to be trained on, and sparse or non-representative data can lead to unreliable outcomes.

Currently, there are some applications of AI in cancers in CTYA but the use is mainly for predicting aggressiveness or treatment outcomes rather than focusing on early diagnosis. In terms of early diagnosis, the main applications of AI would potentially be in identifying high-risk populations and enriching the populations most likely to benefit from screening or advanced imaging tests. For example, various studies have used AI to identify blood biomarkers of early cancers such as long, colon and breast in adults: similar approaches could be used to refer high-risk CTYA for imaging tests but research is lacking.

Other insights:

There are various sources of best practice guidance produced for specific CTYA cancers. One study using a Delphi consensus process developed sixty-four new evidence-based statements on best practice, assessment, imaging and referral of children and young people presenting with key bone and abdominal symptoms[9].

Another study by the same research group, also using Delphi consensus process, developed an infographic for recognising and referring potential childhood bone tumours in primary care, alongside communication advice[10]. Both of these studies are part of the

[9]Shanmugavadivel D, Liu JF, Gamble A, Polanco A, Vedhara K, Walker D, et al. Assessing and investigating children with suspected bone and abdominal tumours: an e-Delphi consensus process. BMJ paediatrics open [Internet]. 2023 Mar 1 [cited 2024 May 29];7(1):e001771. Available from: https://pubmed.ncbi.nlm.nih.gov/36868779/
[10]Shanmugavadivel D, Liu JF, Ball-Gamble A, Polanco A, Vedhara K, Nathan P, et al. Childhood bone tumours in primary care: helping GPs to identify "the needle in the haystack." The British Journal of General Practice: The Journal of the Royal College of General Practitioners [Internet]. 2023 Aug 1;73(733):377–9. Available from: https://pubmed.ncbi.nlm.nih.gov/37500459/

ChildCancerSmart project. There are also many review articles which weren't in scope for this piece of work, but highlight symptom presentation and diagnostic advice[11].

Suspected Cancer Referral Guidelines: NG12 and SRG

NG12	SRG
Neuroblastoma Consider very urgent referral (for an appointment within 48 hours) for specialist assessment for neuroblastoma in children with a palpable abdominal mass or unexplained enlarged abdominal organ. **Retinoblastoma** Consider referral for ophthalmological assessment using a suspected cancer pathway referral for retinoblastoma in children with an absent fundal ('red') reflex. If there is new-onset squint that occurs together with an absent fundal ('red') reflex, see the recommendation on new-onset squint with loss of fundal 'red' reflex in NICE's guideline on suspected neurological conditions. **Wilms' tumour** Consider very urgent referral (for an appointment within 48 hours) for specialist assessment for Wilms' tumour in children with any of the following: • a palpable abdominal mass • an unexplained enlarged abdominal organ • unexplained visible haematuria.	• Unexplained petechiae or purpura is always an indication for emergency referral. • Unexplained fatigue, persistent pallor, failure to thrive or weight loss. • Any new persistent unexplained pain, particularly back pain or nocturnal pain. • Unexplained abdominal mass or distension. • Unexplained visible haematuria. **Bone pain, especially if:** • diffuse or involves the back • persistently localised at any site • nocturnal pain • limping • requiring analgesia, or • limiting activity **Lymphadenopathy, if:** • non-tender, firm/hard and greater than 2cms in maximum diameter • progressively enlarging

[11] Hiller C, Wegler JL, Forest CP. Osteosarcoma: Accurately diagnosing this bone-chilling disease. JAAPA [Internet]. 2016 Dec 1 [cited 2022 Oct 26];29(12):29–35.

Non-site specific symptoms of concern in young people:

Take into account the insight and knowledge of parents and carers when considering making a referral for suspected cancer in a child or young person. Consider referral for children if their parent or carer has persistent concern or anxiety about the child's symptoms, even if the symptoms are most likely to have a benign cause.

Leukaemia in children and young people

Refer children and young people for immediate specialist assessment for leukaemia if they have unexplained petechiae or hepatosplenomegaly.

Offer a very urgent full blood count (within 48 hours) to assess for leukaemia in children and young people with any of the following:

- pallor
- persistent fatigue
- unexplained fever
- unexplained persistent infection
- generalised lymphadenopathy
- persistent or unexplained bone pain
- unexplained bruising
- unexplained bleeding.

Non-Hodgkin Lymphoma

Consider a very urgent referral (for an appointment within 48 hours) for specialist assessment for non-Hodgkin's lymphoma in children and young people presenting with unexplained

- associated with other signs of general ill health, fever or weight loss
- involves axillary nodes (no local infection or dermatitis) or any supraclavicular lymphadenopathy

Headache, if increasing in severity and frequency, and:

- worse in the morning or causing early wakening or
- associated with vomiting or any new neurological signs

Any new neurological signs (weakness, loss of balance etc), especially if associated with behavioural change or deterioration in normal daily or school performance

Other possible signs of brain tumours:

- increasing head circumference
- failure of fontanelle closure
- abnormal head position such as wry neck, head tilt or stiff neck

Soft tissue mass, if:

- shows rapid or progressive growth
- size greater than 2cm maximum diameter
- deep to fascia, fixed or immobile, regardless of size
- recurrence after previous excision of sarcoma
- associated with regional lymph node enlargement

Eyes, if:

lymphadenopathy or splenomegaly. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **Hodgkin Lymphoma** Consider a very urgent referral (for an appointment within 48 hours) for specialist assessment for Hodgkin's lymphoma in children and young people presenting with unexplained lymphadenopathy. When considering referral, take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss. **Bone sarcoma in children and young people** Consider a very urgent referral (for an appointment within 48 hours) for specialist assessment for children and young people if an X-ray suggests the possibility of bone sarcoma. Consider a very urgent direct access X-ray (to be done within 48 hours) to assess for bone sarcoma in children and young people with unexplained bone swelling or pain. **Soft tissue sarcoma in children and young people** Consider a very urgent, direct access ultrasound scan (to be done within 48 hours) to assess for soft tissue sarcoma in children and young people with an unexplained lump that is increasing in size.	• any new squint, if associated with headache or other neurological signs (otherwise consider optometrist and ophthalmology assessment) • change in pupillary red reflex to absent or white Good practice points: Consider referral for any patient with repeat presentations (three or more times) of any symptoms which do not appear to be resolving or following an expected pattern, taking into account parental or carer and patient concern. In a child where symptoms and signs do not clearly fit with these guidelines but nevertheless lead to concern about excluding cancer, the referrer should consider discussing the case with a senior paediatric colleague at their earliest convenience. Many of the tumour specific guidelines in this document are relevant to all ages e.g. melanoma, brain and CNS, sarcoma etc.

Consider a very urgent referral (for an appointment within 48 hours) for children and young people if they have ultrasound scan findings that are suggestive of soft tissue sarcoma or if ultrasound findings are uncertain and clinical concern persists.	