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Improving identification of cancer in young people: a scoping review

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Improving the identification of cancer in young people: A scoping review.

Abstract 180/200

Introduction: The challenges of achieving timely cancer diagnosis in adolescents and young adults are recognised. However, contributing factors and associated clinical and psychosocial outcomes are poorly understood.

Areas covered: We present a scoping review of existing evidence into time intervals to diagnosis and potential mechanisms influencing the identification of cancer symptoms and impact on a timely diagnosis. Charting data using Walters 'pathways to treatment' we summarise the diagnostic pathway into four interval categories: appraisal, help-seeking, diagnostic, and pre-treatment, and illustrate where evidence exists and where unanswered questions remain.

Expert commentary: Whilst the research base has expanded over the last decade in cancer care there continues to be limited research that reveals the complexity of the timeliness of diagnosis in this population. There are unique issues facing this age group in terms of rarity of cancer, complexity of symptoms and problems with healthcare system access that create a constellation of challenges. We offer explanations for diagnostic difficulties in this age group, and explain how, with the limited available evidence, we are still seeking solutions to what is a uniquely complex problem.

Key Words: Teenagers; adolescents; young adults; timeliness of a cancer diagnosis; pathways to treatment; scoping review

1. **Introduction**

A diagnosis of cancer is a significant life event for anyone, but perhaps more so for adolescents and young adults (AYA's), as they are at a particularly vulnerable developmental stage [1]. The adjunct of a potentially life threatening diagnosis with the normative developmental tasks of adolescence can have an adverse impact on AYA's physical and emotional wellbeing: this potential impact can be profound. The symptoms of cancer, superimposed on the anxiety of the period leading up to a diagnosis, can evoke psychological distress, uncertainty and fear in young people. Many describe their diagnostic experience with a sense of loss, anger, and frustration [2]. However, with a definitive diagnosis the process of renegotiating a new sense of identity and place in the world can begin. Young people, using social media, have also described trying to make the best of their situation, finding ways to overcome negative emotions and an urgency to return to normal as soon as they could, even if this was to a 'new normal' [3].

Improving both the experience and outcomes of a cancer diagnosis through earlier intervention has become the focus of national policy in the United Kingdom [UK] [4-6], in the United States [US] [7], as well for international AYA clinical partnerships [8]. Specific to the UK context there are two relevant health policy initiatives. First, the 'two-week wait', introduced in 2000, whereby anyone with a suspected cancer would be referred to a specialist within fourteen days [9]. Second, the National Awareness and Early Diagnosis Initiative [10], introduced in 2008, that continues to spearhead an increased focus on the importance of earlier diagnosis and its potential association with reduced morbidity and mortality in some cancers [10]. It is recognized, however, that precisely quantifying the relationship between the time taken to diagnosis and survival is challenging but it is known that, for some cancers at least, a shorter time to diagnosis is associated with a poorer outcome [11]. Despite this, there is a general consensus that optimizing the time from symptom onset to a definitive cancer diagnosis is a worthwhile pursuit [5, 12-17]. Not least this is because strength of the patient voice across the cancer population suggests that 'rapid and adequate referral' is an important measure of quality [18], and subjective experience of high quality care [19]. Delayed and/or multiple referrals are associated with a greater chance of decreased confidence in either the patient's General Practitioner (GP) or another referring clinician [20,21]. Patterns of referral, and the subsequent patient journey, have been studied in the UK with the most common route to diagnosis for older adults aged between

50 and 79 being the two week urgent GP referral for suspected cancer [22]. In contrast the most common route for those aged 15-24 is via non-two week wait GP referrals (26%), followed by emergency presentation at Accident and Emergency [A&E] Departments (24%). In this first report only 13% of AYA were diagnosed via the two-week wait initiative suggesting minimal impact from this earlier referral policy for this population [23]. However, the most recent National Cancer Intelligence Network data would suggest that while the most common routes to diagnosis are still via non-urgent GP referral (28%) and A&E admissions (26%), the proportion being diagnosed by urgent two-week referral has increased considerably to 22% reflecting a change in practice, and perhaps greater awareness of the unique needs, of this age group [24]. The association between A&E cancer diagnosis-related admissions and poorer outcomes has not been confirmed in AYA and insufficient data exists, however the nature of presenting symptoms for some young people's cancers may mean that A&E will be their first point of entry into the healthcare system.

The NAEDI campaign in the UK also includes a focus on improving help-seeking behaviours through screening, self-examination and the promotion of better cancer awareness [25-27]. The latest UK campaign 'Be clear on cancer' [28], stresses the link between early diagnosis, higher success of therapies and improved quality of life for patients. However, the relationship between greater awareness, better cancer-related knowledge, improved interpretation of symptoms, and the subsequent positive impact on timely access to health-care, and hence effective and timely therapies, is a complex mix, and these various factors are only beginning to be examined in the AYA population [29-30]. Hence there exists a continuing need to drive a national ambition to achieve earlier diagnosis. Indeed, this is one of the six strategic priorities from the UK Cancer Taskforce [31], being implemented through the ACE program: Accelerate, Coordinate, Evaluate [32], exploring innovative concepts in early diagnosis pathways.

Much of the existing evidence regarding the time to diagnosis has been generated from research with adult cancers; limiting its generalisability to the AYA population. The existing evidence, therefore, provides little in the way of easily identifiable solutions to improve the timeliness of a definitive diagnosis for this population. Part of the explanation for this situation is related to deficits in the quality (as well as quantity) of published research which may be difficult to interpret through lack of precise definitions, variations on health systems or lack of reproducible methodologies [33-

34]. However, increasing evidence, from a number of sources, is now emerging that may have greater specificity to younger people with cancer (Table 1). As a result, this ensures that the timeliness of a cancer diagnosis remains close to the top of the UK cancer policy agenda [35].

Given this situation we sought to identify elements of the diagnostic pathway that have already been subjected to analysis. This is in order to contextualise the many factors across the diagnostic pathway, that may influence the practice and timeliness of achieving a cancer diagnosis in AYA groups in the UK, and elsewhere; as well as to inform the focus and direction for future interventional research.

2. Methodology

We undertook a scoping review of the relevant literature. Scoping studies aim to map rapidly the key concepts underpinning a research area and can be especially useful where an area is complex [36]. Such reviews typically do not assess the quality of included studies, but present an analytical reinterpretation of the literature to guide more focused lines of research inquiry [37]. We used the five stages originally described by Arksey and O'Malley [36], and the work by Levac [37] that aim to enhance this review methodology: Stage 1, identifying the research question; Stage 2, identifying relevant studies; Stage 3, study selection; Stage 4, charting the data; Stage 5, collating, summarizing and reporting the results.

2.1 Research question

What is the extent, range and nature of research that best describes what we know about the diagnostic pathway for adolescents and young adults (AYAs) with cancer?

2.2 Identifying relevant studies

Data were identified through searches of MEDLINE, PubMed, OVID and Psychlit, using the search terms "adolescent", "teenager", "young adult", "cancer", "diagnosis" and ''delay''. Papers identified from the search were cross-referenced with cited sources within the retrieved papers so that any otherwise non-identified papers could be included. Relevant policy documents were also accessed by online review and hand searching.

2.3 Study selection

Inclusion criteria:

1. Peer-reviewed research exploring the diagnostic process, including delay.

2. Published in English between 1990 and 2016.

3. Reporting on adolescents and young adults, defined as those between 16 to 24 years in the UK.

4. Reporting on child-AYA or adult-AYA in the same paper.

Exclusion criteria:

1. Reporting on adolescents or young adults, <16 years, >24 years.

2. Reporting a single population of 'adults' or 'child' in a paper.

Copies of the full articles were obtained for those studies that appeared to represent a 'best fit' with our research question.

2.4 Charting the data

One of the most influential models for describing pathways to a cancer diagnosis was proposed by Andersen et al in 1995 [38]. This original model describing 'total patient delay' has been summarised in three overall categories by Hansen et al 2008 [39]: patient delay, doctor delay, and system delay. Historically, patients and professionals have referred to 'delay in diagnosis' and 'diagnostic delay' however, there has been a move away from this terminology due to the negative connotations of 'delay' which may impose guilt and regret from a patient perspective if they have delayed seeking help for a symptom which turned out to be cancer related; it might also imply some degree of blame or neglect on the healthcare professional. The revised model by Walter et al 2012 [40] reflects more acceptable parlance and importantly illustrates that the pathways to diagnosis are often not linear as patients may transverse back and forward along the pathway as diagnostic tests are verified or dismissed [41]. Four categories of the diagnostic process are described [40]: appraisal, help-seeking, diagnostic, and pre-treatment intervals. These categories of interval provided an analytical framework to use when charting our data (Figure 1). Walters model also cites a number of contributing factors which influence these intervals: patient factors (demographics, psychological, social, cultural, previous experience); disease factors (size, growth rate); and healthcare provider and system factors (access, healthcare policy and delivery). Considering each of these factors allowed us to deliberate these in the context of young people and demonstrate how some of the contributing factors are unique to this group. This also assisted us in illustrating where evidence existed and

where unanswered questions remain. The framework was used to chart a narrative summary of information gained from each publication. Charting against this framework helped further in improving our understanding by building on existing knowledge that may be applicable in the real-world context of policy and service development [42] Included therefore are additional publications outside of our search parameters that are thought to be relevant to illuminate the 'whole story' on timeless of achieving an accurate cancer diagnosis in this age group.

2.5 Collating, summarizing and reporting results

Electronic searches revealed a total of 340 articles, 297 were rejected and 43 full copies were retrieved for eligibility assessment. We included all papers at this stage, irrespective of the research methodology, and included editorials, letters, and research reports, if they dealt with cancer and diagnostic intervals in the AYA population. After rejection of a further 18, three additional papers identified through citations were also deemed eligible for inclusion giving a total of 28 papers for review (Figure 2).

The majority of eligible publications included combined data on cancer diagnosis in children and AYAs, and only eight focused specifically on the AYA group as a single population. Table 1 summarizes the main characteristics of the final 28 publications: 19 retrospective and prospective studies on diagnostic intervals, five papers on adolescents' knowledge, awareness and attitudes towards cancer, three systematic reviews and one editorial (n=28).

3. Results

Here we present a narrative summary of the results discussed within discrete headings as per the four intervals in the pathways to treatment (Figure 1).

3.1 Appraisal interval

This is defined as the time from awareness of a bodily change to perceiving the need to discuss symptoms with a healthcare professional, such as a GP, or to make contact with the acute health care system. Appraisal interval has been described in a number of helpful studies spanning child and early adolescent cancers [43-44] This body of research, mostly utilizing retrospective analysis of medical notes and cohort designs, suggests that age appears to be a significant factor [45-46] Those in their

teenage years are more likely to experience a longer interval from initial symptoms to reporting symptoms to healthcare professionals than younger children [46, 47-52]. There is little research as yet to underpin explanations of this longer interval in AYA, however in the context of Walters contributing mediators there are some identifiable and unique factors.

Disease factors: symptom pattern

One possible explanation for the effect of age on a timely cancer diagnosis is symptom pattern. Younger children may experience cancers with more identifiable signs at onset (such as an abdominal mass in Wilms' tumour) than older children or AYAs. However, studies have reported a positive association between age and diagnostic interval still being present even after the type of cancer was controlled for [46, 53-54]. This would suggest that the effect of age on interval may, in part, be due to more than simply differences in tumour-specific characteristics [45]. Appreciating the importance of symptoms that lead to help-seeking behaviours, may lead to a better understanding of the time between symptom onset and diagnostic trajectory. The following risk factors have been identified in the literature to date: symptom recognition, psychological factors, socio-demographic influences and ethnicity [40].

Patient factors: cancer awareness

The initial presentation of possible cancer symptoms, due to rarity and lack of specificity in this age group, has been associated with prolonged time intervals [47, 50, 55-56]. Public awareness of early warning signs of cancer has been identified as playing an important role in symptom recognition (although it has also been identified as a prompt for seeking medical help by the 'worried well') [55, 57]. Two studies in the UK have shown that cancer awareness in adolescents is low [58-59]. In both studies adolescents did not know the most common cancer in the AYA age group, and there was also the belief that cancer was unrelated to age [28]. In a cross sectional study in the UK [29], teenagers recall of cancer signs was good for lump/swelling, but their recall of other cancer warning signs or symptoms was very poor (13.8% for both 'unexplained pain' and a 'change in the appearance of a mole', 6.5% for 'weight loss' and 1.3% for 'a sore that does not heal') and one in four young people could not name a sign or symptom of cancer. Moreover, studies from the UK, United States, Turkey and The Netherlands have shown that self-examination for signs of cancers found in AYAs is also poor [59-62]. For example, the number of young males knowing how to, or who have performed, testicular self-examination was low [59-61] as was female adolescents' knowledge of breast self-examination

[62].

Health knowledge has been found to be a contributing factor in diagnostic processes and a lack of knowledge has been linked to AYA's intentions to delay health care seeking, even when signs and symptoms are present. It has been shown that adolescents who have never heard of testicular self-examination were more likely to report the intention of putting off health care seeking with symptoms of testicular cancer [63]. Conversely, three quarters of adolescents taking part in a Survey (Cancer Awareness Measure [CAM]) stated that they would seek help for a symptom they thought might be cancer within three days [29]. Hence, empowering AYAs for greater self-care and early detection of cancer are important and seem to be worthwhile pursuits [64]. It has been suggested that health education within schools should also reflect cancer topics including the importance of early recognition of possible signs and symptoms [58]. School environments provide fertile ground for public health campaigns, particularly when the materials used are age specific to aid relevance and retention [30].

Patient factors: demographics and psychosocial

Longer intervals from initial symptoms to the reporting of symptoms to healthcare professionals, when compared with younger children [44, 46, 47, 51], may be explained by a range of demographic and psychosocial factors. Young people's strong sense of independence and sense of invincibility may lead to a decrease in parental influence over this age group as well as to an undervaluation of symptoms; hence AYAs may be more likely to delay attracting attention to themselves [64]. In-depth interviews about young people's pre-diagnostic experiences has shown that they may normalize or wrongly attribute their symptoms to something other than cancer, and other people (such as parents, teachers, neighbours or co-workers) may play a significant role in prompting them to have troublesome symptoms investigated [65]. Gender-associated behavior expectations may also influence a longer appraisal interval, however findings have not been consistent, with one study reporting that males diagnosed with a medulloblastoma experienced a longer duration of symptoms than females [66]. Moreover, a powerful social desire to appear 'normal' and 'independent' often associated with adolescence may also contribute to a reluctance to trust adults – including the medical establishment [49]. Nevertheless, contrary to perceptions that AYAs may generally have less contact with health care services, Fern et al.'s study [67] found that this age group do indeed consult

with GPs with symptoms. Thus young people do consult their GP, however this is generally for routine non-cancer reasons such as contraception and pregnancy and infection [67].

Overall, research evidence into the appraisal interval shows that from first symptom to consultation with the healthcare system is not a straightforward process. Age may indeed have been associated with an increased time interval, but age alone is insufficient to 'truly' understand prolonged symptom appraisal. Attitudes, beliefs and social context clearly also influence the process of making a decision to seek help. Increasing cancer awareness may deserve to be an important national health policy imperative: as simply being able to talk about cancer is one determinant of medical help-seeking [68].

3.2 Help-seeking interval

Patient factors: psychological

This refers to the interval from perceiving a reason to share symptoms with a healthcare professional to the first consultation. Within the adult literature recent findings have shown cross country comparisons with adults putting off going to the doctor as they do not want to 'waste the doctors time'. For young people emotional barriers to help-seeking were actually the most commonly endorsed behaviours by more than half of participants in one study of cancer awareness ('worry about what the doctor might find', 'too embarrassed', 'too scared', and 'not feeling confident to talk about symptoms'), followed by service (e.g., 'difficulty talking to the doctor') and practical barriers (e.g., being 'too busy') [30]. Similar findings have been described with an Italian population of adolescents. They also described not wanting to alarm their parents, and avoided the need to have their body examined or touched by adopting a 'wait and see approach' [69]. A similar approach was also reported by Dixon-Woods et al [70]. In this study, parents did not want to appear 'anxious', 'overprotective' or 'neurotic' by consulting a GP too often or too early. Thus most parents adopted a 'wait and see' approach for mild symptoms e.g. viral symptoms, sore throat, or tiredness. General Practitioners also discussed fear as the single most important factor, both consulting and delaying, with a good professional/patient relationship being a prerequisite for patients' concerns being taken seriously. Patients' accounts of their experiences prior to their diagnosis also show the importance of this relationship. When young people were well known to the GP, action seemed to be taken more quickly; conversely the lack of relationship had a negative influence on AYA's chances of been taken seriously [65]. Hence, the lack of routine care prior to any cancer symptoms, as well as any co-

existing communication barriers, may have an impact on the relationship between patients and

professionals and consequently on a timely diagnosis [49]. The differences described in barriers to

help-seeking behaviour provides further evidence as to why studies carried out with adult

populations cannot always be extrapolated across AYA's and why they should be studied as a unique

group.

Patient factors: age and social

Exchanging opinions with peers, and seeking information online may also represent early steps in

seeking help that avoids the need to consult with healthcare professionals directly [69]. Adolescents

in the 21st century rely on technology much more than their adult counterparts for communication,

accessing information, and generally, living life (e.g., using social Web sites, texting, and messaging)

[71]. Thus these avenues may offer other routes for health information that avoid the need to ask

questions of professionals, or communicate their fears by providing privacy, ease of access and even

a sense of community [72-73]. The unreliability of some Internet content however is a concern for

many AYAs [74]. At the current time, there is a substantial knowledge gap in the Internet on the

matter of cancer in our population [69].

Healthcare provider and system factors: access

Access to medical care in some countries can also influence duration of the help seeking interval

(e.g., in the US some young people are not covered by parents' health insurance) [49, 75]. For others

social services barriers, such as being on income support, or unemployed, and having personal/family

stability have also been described in terms of inequalities that impact on the diagnostic pathway [76].

In some countries the primary physician for children and AYA is a pediatrician, not a GP, where

familiarity with cancers that occur in this age group may reduce the time to diagnosis: both health

care systems and geographical differences are factors also known to affect the symptom interval and

patient delay [77].

Overall, research into the help-seeking interval is limited. There is however much we can learn from

adolescents as a population. We know that their health issues may be less closely monitored by their

parents when compared to younger children, and we know they may be reluctant to talk openly

about, and hence disclose, worrying symptoms that they may be experiencing. Lack of awareness

about health risks and their changing bodies, poor knowledge and limited experience of the

healthcare system or how to access it, compounded by social and societal influences combine to

impact negatively on help-seeking behaviours. Possible solutions, such as improving cancer

awareness, are relatively inexpensive, as well as making more communication opportunities available

so that AYA's can find accurate information about worrying symptoms.

3.3 Diagnostic interval

This refers to the interval between first consultation with a healthcare provider and a cancer

diagnosis being made. This may involve referrals for diagnostic tests or to specialist services.

Healthcare provider and system factors: access, healthcare policy and delivery

The type of healthcare professional contacted initially has been reported as having a direct impact on

the length of this interval (44, 45, 46, 47, 77-80]. For example, longer intervals have been reported

for those presenting to their GP compared to Accident & Emergency (A&E) departments. In Dang-Tan

et al's study [48] into children and adolescents with leukaemia and lymphomas in Canada, longer

diagnostic intervals were found after referral to secondary care; patients first seen in a hospital

emergency room also had a lower risk of delay than patients first seen by a GP. Presentation to A&E

more commonly led to immediate X-rays than a GP consultation. It has been claimed that these

increased intervals are not necessarily a reflection on GP's actions (or inaction) but may exemplify

the weaknesses within the process of referral from professional too professional [81]. Parents may

try to speed up this process with the use of private medical services, accessing alternative medicine

or by resorting to A&E departments for immediate advice after failed referrals from primary care

[68].

The prompt referral for a suspected cancer symptom from primary care is known to be challenging

for this age group [80]. Reasons are not entirely clear, but may include atypical presentations,

suboptimal clinical reasoning or other healthcare factors [82]. Young people have reported repeated

interactions with a range of health care professionals when seeking a diagnosis, including

optometrists, dentists, pediatricians' and other specialists [83]. A retrospective Italian study between

September 2007 and March 2011, reported that the lag time between seeing a physician and being

referred to a specialist was longer for teenagers compared to children [84]. Young people have repeatedly reported multiple consultations prior to referral to a cancer specialist during an annual patient conference and this has recently gained further substantiation following analysis of the NHS Cancer Experience Survey [81,85]. Importantly young people aged 16-24 are twice as likely to have three or more consultations prior to referral compared to older adults. Approximately 40% of young people will consult three times or more prior to referral compared to 20% of older adults, thus 80% of older adults are referred on their first or second visit. Diagnosis via the A&E route has become associated with AYA experiencing repeated cycles of appraisal and help-seeking [86]. Referral guidelines for children and young people have been developed recently as a result, and are now in their second round of revisions (87-89). Evidence suggests from young people themselves however that there remain challenges when applying the guidance to AYA, or where there is a NICE qualifying symptom this may not always result in referral, and sometimes referrals were made but investigations did not occur [90]. Thus, the importance of the AYA cancer diagnostic interval continues to be recognised as inherently complex and an area worthy of further exploration [45, 46, 85,90].

Disease factors: symptoms and types of cancer

Quantitative studies using survey methods have shown that longer diagnostic intervals (rather than appraisal or help-seeking intervals) have been reported by AYAs [69]. This is also true in relation to cancers more often occurring in this age group, such as bone and soft tissue sarcoma and lymphomas [48]. Dang-Tan et al study [49] found that timeliness to diagnosis of bone cancers was influenced by longer diagnostic interval but shorter appraisal interval. Short appraisal interval and longer diagnostic interval and misdiagnoses have also been identified in a review of medical charts in South Africa [91].

Many physical signs and symptoms of young people's cancers such as fever, headache, fatigue, bone pain and weight loss may be attributed to more common problems such as, sporting injuries, stress and general fatigue [58, 79]. Pollock et al [46]. In a retrospective, multi-centred, study of children with a lymphoma or solid tumour, found longer lag time or symptom interval (time between presentation and diagnosis) in Hodgkin's disease and bone sarcomas (particularly Ewing's sarcoma) than in those with brain tumours or non-Hodgkin's lymphomas - the shortest lag time was for those children with neuroblastoma. Even after adjustment for age in a multivariate analysis of covariance, tumour type continued to have a statistically significant association with interval [46]. Factors may

include the slow-growing nature of Hodgkin's lymphoma and Ewing's sarcoma; their peak incidence being in the second decade, together with an often longer diagnostic process compared to some other cancers [12]. In Dang-Tan et al.'s study [48], cancer subtype was associated with diagnostic interval - but not with patient appraisal - for lymphoma patients. Patients with non-Hodgkin's lymphoma had longer delays as those with Hodgkin's disease. In this particular case, the differences between disease symptoms and signs for these two different forms of lymphoma may have contributed to this difference. Goyal et al [44]. study found that the site of the tumour (axial vs. limb) affected diagnostic interval in that the same symptoms in the absence of an obvious 'visible mass' did not seem to alert the suspicion of the healthcare professional in the same way that limb-associated symptoms did. This is similar to other studies where more unusual symptoms (such as gait abnormalities, ataxia or abdominal masses) also had a shorter time interval [51].

Healthcare provider and system factors: healthcare policy and delivery

Although there has been less research about the in-depth experiences of healthcare professionals and why they may not suspect a cancer, it has been shown that several factors may impact on this situation. These include: perceptions of symptoms and the implications of the socio-economic status and age of the patient; past experiences with diagnosing cancer (it may be rare for GP to see AYA with cancer - a GP in the UK, for example, may be expected to see, on average, only one child under 15 with cancer every 15 years [81] or only 7 to 8 new cases of cancer, in all age groups, per year); and structural issues such as lack of time, lack of team working, lack of consistency in seeing patients, poor follow-up mechanisms and missed communications between different settings. These may all be considered important and relevant to the reasons for diagnostic delay in AYAs [89].

Moreover, although there is no evidence at present that lack of knowledge or awareness about AYA cancer is related to increased healthcare professional time intervals, it has been suggested that training in AYA cancer diagnosis could be beneficial in improving the recognition of classic cancer symptoms [83]. However, many will present with what are described as symptoms that have low or very low positive predictive values; and are often non-specific and vague in nature. Thus the 'alarm' symptoms - such as pain or physical changes – [92] that may generate a risk assessment in adult cancer care [93], are not always present or reliable in this population [94]. Presenting with non-alert symptoms, as categorized in the NICE guidance [88], is known to increase the diagnostic interval [95].

As part of a national audit of cancer diagnosis in primary care in the UK, 40% of young people who were identified attended the GP three times or more before being referred [96]. A significant event audit carried out under the aegis of NAEDI illustrated that GPs themselves spoke about the difficulties in engaging, and obtaining a diagnosis with this age group, and mentioned the perceived reluctance of some young people to seek advice. The importance of professional vigilance, effective communication and the appropriate management of unresolved symptoms have also been highlighted within the existing literature and remain relevant [96].

Young people themselves in in-depth interviews have also suggested that a wide variety of intervals to diagnosis are a recurring element of some young people's cancer trajectory [65]. For instance, some have reported not being taken seriously, not having their concerns addressed and often feeling that healthcare professionals might not attribute their ongoing symptomatology to cancer [65]. These findings suggest that young people were often not investigated for cancer until after they had visited their doctor several times, or until they, or their parents, also started to think something more serious was wrong. Young adults have expressed the opinion that GPs should consider serious illness earlier, even if it seems unlikely [65].

The period prior to diagnosis is important in shaping the nature of adaptation and the subsequent reaction to the diagnosis itself [70]. Qualitative studies in childhood cancer focusing on parents' recall of the diagnosis of cancer in their child [70, 97, 98], suggest that difficulties in reaching a diagnosis has the potential to cause friction in the GP/parent relationship [99]. This is particularly so when parents did not think their concerns had been listened to [97]. Similar findings have been reported with the AYA age group [65]. Perceptions about diagnostic intervals are clearly significant, with a considerable overlap in the time reported by parents who felt that the diagnosis was not timely, as compared to those who did {97]. Patient confidence is known to be a core element of the doctor-patient relationship: and further research is needed to understand the impact the period prior to diagnosis has on this relationship in the long-term [99].

Overall, we would agree with Black et al (86 p13) that the pathway to receiving a cancer diagnosis in AYA's may be both 'prolonged and circuitous'. Where a GP route has not resulted in resolution, AYA may engage with other routes, such as A&E, where tests might be more rapidly forthcoming. NICE guidance [88], as it currently stands, might not assist with the nuances and differences in AYA's as

they do not take full account of the many contributing factors (identified by Walters) that present as challenges to GPs and others.

3.4 Pre-treatment interval

This refers to the interval between a definite diagnosis being made and the initiation of cancer control treatment. This is the part of the cancer trajectory where there has been the least research. It has been recognized, and this paper has already demonstrated, that prompt diagnosis and referral for treatment in AYA can be challenging from a clinical perspective, due to the wide range of malignancies and the multiplicity of symptomatologies that may arise. Cancers in AYA can be classified into three main categories: those that typically arise as 'late paediatric' cancers such as Wilms' tumour; those that are described as 'early onset adult cancers' such as melanoma; and those which have a peak incidence in this age group alone such as osteosarcoma [100]. The most common cancers in adults comprise only a small proportion of cancer diagnosed in AYA; nevertheless, cancer type has been associated with pre-treatment interval and lymphomas, bone tumours and soft tissue sarcomas. which have a higher incidence in this age group, typically require molecular and other diagnostic tests before administering first treatment [47]. Papers have identified delays in the detailing of histological sub types [49, 91]; delays in both the referral to and correct reporting and communication from imaging [79, 104]; and delay in referrals to the correct specialist [65, 81, 101].

Poor communication between services, poor reporting of results and the waiting for appointments was found to be particularly stressful for young people, especially after a diagnosis of cancer had been made [65]. In Klein-Gletink et al's study [101] (where outcomes were compared between adolescents treated in adult-orientated and child cancer centres) the interval for referral of AYA to adult-orientated centres was found to be twice as long as those for childhood cancer centres.

Whilst this may be the least researched phase of all across the cancer trajectory it remains important as negative psychosocial reactions may be expected following cancer delay, or where disease is much more advanced meaning that treatment is less likely to be curative [65]. It is also a phase where positive relations can be established that can support the young person going forward into cancer treatment.

These structural, organisational, resource and pathway related issues have generally been less researched across all age groups but certainly warrant wider scale attention and programmes of work in the future.

4. Limitations of this review

As this was a scoping review some papers may have been missed during the literature searching process. If a full systematic review had been undertaken more databases would have been searched and could have identified additional relevant studies. However, we suggest that the review captures the state of the art in this field of research, with the remaining areas for future research clearly identifiable.

We were also well aware of the methodological limitations of some of the research in this field that have been well-documented [33,34]. Others have criticized research designs where information collected through pre-existing records and/or patient/parent recall may not always be reliable [34]. Identifying possible sources of diagnostic delay from the perspective of patients and healthcare providers is uniquely challenging due to symptom/disease complexities as well as the many steps involved in the diagnostic trajectory superimposed on complex health systems. An earlier review [102] emphasized the danger of attributing simplistic solutions to inherently complex phenomena. The studies included here share and reflect these limitations. Furthermore, difficulties are acknowledged in terms of the lack of research where the AYA age group have been studied as a discreet group. Most papers do not focus specifically on this specific age group meaning that some evidence has been drawn from studies of childhood cancer that included AYA in their populations in recognition of their contribution to the conclusions.

5. Expert commentary

Whilst the research base has expanded over the last decade in AYA cancer care there continues to be limited research that reveals the complexity of the timeliness of diagnosis in this population. There are unique issues facing this age group in terms of rarity of cancer, complexity of symptoms and problems with accessing the healthcare system that creates a constellation of challenges (Figure 3). Given this complexity our use of a methodological framework to structure charting and analysis of the literature has enabled a fuller description of the importance of the various interval factors to be understood and examined further. In terms of the particular needs of the AYA age group, this review has highlighted the importance of understanding the significance and range of factors such as

attitudes to health care, the nature of cancer symptoms, information needs and the social reality of young people's lives, that combine to impact negatively on timely help-seeking behaviour and eventual diagnosis.

Given the relatively rare incidence of cancer in the AYA population, superimposed on the complexity of primary and secondary health care systems, it is perhaps not surprising that a prolonged diagnostic pathway may occur in this age group. The existing evidence points to a combination of ways to firstly theorise and understand, and then improve, the diagnostic experience for younger people facing cancer. Here the evidence has been used to clarify what changes may be possible to modify in a positive way (such as greater AYA, parent, public and professional awareness; communication between services; and timely access to care) and to highlight others that remain problematic (such as vagueness of symptoms or health system failure). The threat of a cancer diagnosis or serious illness does not sit easily in the everyday world of AYAs. As a result, further research is needed to better understand how to improve outcomes by tackling the first two stages of symptom appraisal and help-seeking by concentrating on assessing the need to seek professional help and motivation to attend the first appointment.

The interval between the first consultation with a healthcare provider and a cancer diagnosis has often been seen as significant in the time to diagnosis. It may involve repeated visits before anything serious is suspected, and time being taken up for referral to diagnostic tests or to specialist services. Having key healthcare professionals respond, and allowing AYAs to have a voice and be heard, are key components to this stage of the AYA cancer trajectory. However, we currently have little empirical information about the impact of multiple consultations on young people. It must also be remembered that for many GPs it may be that clinical reasoning was appropriate as in many cases benign conditions were eliminated. Indeed, the healthcare professional, structural, disease and symptom related factors that contribute to this time interval exemplify why the time to diagnosis may be complex and prolonged and further support the need for evidence-based solutions. Although there is less research in this area, and the prognostic implications of lengthened diagnostic time intervals are not always clear, the link between time intervals and an increase in psychological stress in AYA's is apparent.

For instance, it is known that prolonged periods to diagnosis have been found to have a significant clinical impact in terms of raising levels of anxiety, uncertainty and coping in children [51, 98]. Gibson et al's [65] study pointed to the importance of young people feeling that they had a voice, and that their symptoms and worries and concerns were heard, and when they were not, a significant lack of trust and anger could develop. Tishelman and Sachs [103] found that after a process of constant negotiation between popular and professional judgements, an eventual diagnostic outcome provided the opportunity for a new framework of 'normality'. Similar findings emerged from an interview study with AYA and nurses on the distressing and positive experiences of cancer. Over half responded that a definitive diagnosis was better than pre-diagnostic uncertainty, with hope becoming more realistic once the prognosis and treatments were explained [104].

Timeliness of a cancer diagnosis and the emotion it brings can thus have significant repercussions for coping during the diagnostic period, treatment and adaptation to life after treatment. As mentioned earlier there is very little research as yet for AYA in the pre-treatment phase, but after a diagnosis of cancer, this is something which should addressed in future research. In the UK, healthcare providers are assessed on the ability to provide cancer treatment within a certain time. The current target waits between the date the hospital receives an urgent GP referral for suspected cancer and starting treatment; starting treatment no more than 31 days after the meeting at which AYA and a medical healthcare professional agree the treatment plan. If patients are delayed in the pre-treatment phase it maybe to clarify precise details of tumour biology and pathology, making complex treatment plans or identifying clear treatment pathways. http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/waiting-times-for-tests-and-treatment-after-cancer-diagnosis#treat) Generally hospitals are meeting this target for most of their patients. Although as Klein-Gletink [101] state there are differences in this phase for AYA going to a children's cancer centre as opposed an adult cancer centre. The reasons for this are unclear but may include lack of established care pathways, less specialist nature of care in general adult compared to children's cancer together with the possibility of different diagnostic groups and diagnostic pathways in adult and children's cancer centres.

6. Five-year view

Understanding the reasons that impact on a timely and accurate cancer diagnosis is important for all

age groups and, in this population, would benefit from further research focused on the perspectives of young people themselves, the healthcare professionals who care for them, and research into structural and organisational barriers for timely access, referral and diagnosis. Such evidence ultimately needs to be strengthened by considering the range of data needed, such as diagnostic timelines; symptom profiles and disease outcomes; professional perceptions and roles; and service, referral and communication barriers - within the context of current service or policy developments: in the UK and elsewhere. Complex and multi-factorial phenomena, such as the diagnostic process, are likely to require complex, multi-method, multi-perspective research approaches. With the subsequent development of appropriative interventions (Table 3) and changes in practice and policy, it may be possible that under-researched patient groups such as AYAs may achieve more timely diagnoses of cancer.

In the meantime, we have to consider the pressures on health systems to process more demand, both in general practice and in hospital contexts, and AYA cancer care is only one of the multiple demands facing providers. Given this situation it is also important to contextualise what research will be needed to understand health systems as inherently complex and inter-connected, and where promoted values such as psychological adaptation to cancer, holism and patient safety must co-exist alongside concerns with service efficiency and cost-control.

We suggest that the existing research is already highlighting the existence of a problem with AYA cancer diagnosis that needs to be addressed in a number of ways. Firstly, policy is needed, based on evidence, that will help enhance access to age appropriate information and support. Secondly, research should build on existing gaps and address the most pertinent questions that should be asked to improve the diagnostic experience. Reviews such as this can help in this regard and more research is now being supported; such as the Lymphoma Research Foundation in the United States which has an AYA funding initiative.

Finally, the views of young people themselves should remain at the heart of accounts of where systems can be seen to encourage, or deter, them from seeking help. The third sector has a key role to play here and much opportunity exists for charities and lobby groups to influence awareness of the signs, symptoms and diagnostic trajectory for cancer across all age groups: for example, in the UK an online educational resource has recently been developed through the collaboration of two UK

charites http://elearning.rcgp.org.uk/course/info.php?id=232 [105]. For the AYA population this review has highlighted the growing evidence that can be used to understand their needs in being diagnosed as quickly as possible in order to effect the best possible outcome.

Key issues

- Non-specific presenting symptoms, low awareness, system failures and rarity of cancer in this population impacts on the timeliness of achieving a cancer diagnosis.
- Effective communication, with an emphasis on diagnostic uncertainty in discussions between healthcare professionals and AYA, is essential so that AYA fully understand the decisions that are made.
- Adolescents and young adults must be encouraged to return to their GP if symptoms escalate: re-appraisal of symptoms and help-seeking is not linear.
- The prognostic implications of a possible time-lag remains unclear.
- Lack of AYA awareness about themselves and their bodies, their community and health care systems impacts on elements of the diagnostic pathway.
- The support needs of parents and those closest to these young people is important as they also face the challenge of a cancer diagnosis.
- Untimely diagnosis affects the overall patient experience negatively, and may not place the AYA in the best position in terms of future relationships with primary or specialist cancer services.

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Figure 1. Model of pathways to treatment
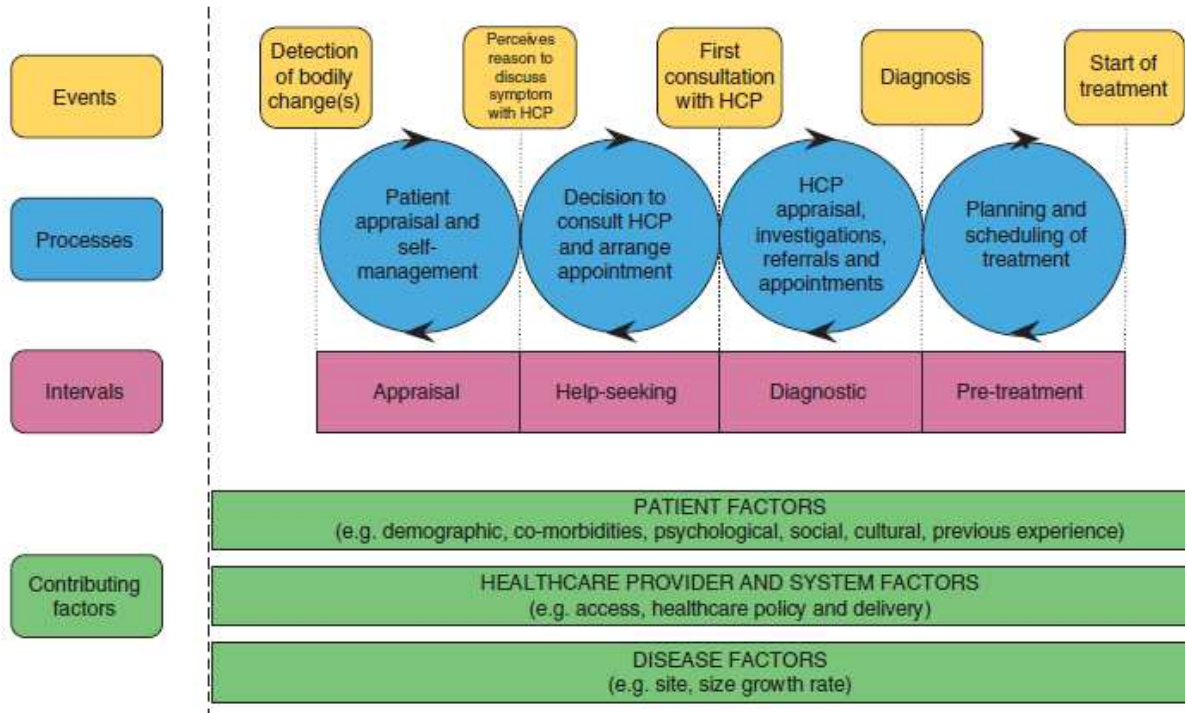
From Walter et al 2012

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Figure 2. Scoping studies

Titles identified and screened
n= 340

Excluded
n=297

Full copies retrieved and assessed for eligibility
n= 43

Excluded
n=18

Studies that met the inclusion criteria
n=25

Identified through citation
n=3

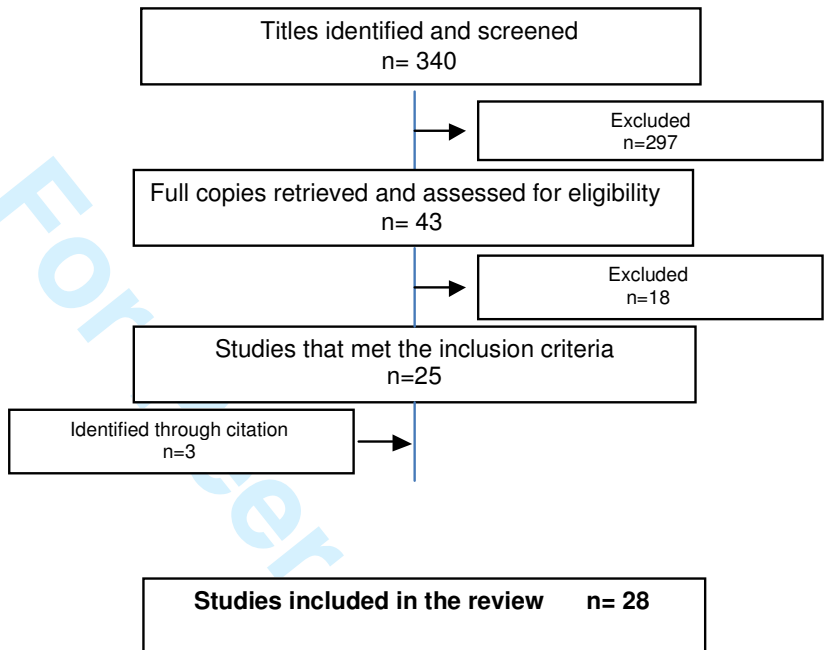**Studies included in the review   n= 28**

Figure 3: Factors affecting pathways to cancer diagnosis for adolescents and young adults

Disease factors

Cancer related
- Rare cancers
- Non-specificity of symptoms
- Symptom pattern
- Site of cancer

Physical factors
- Puberty
- Normal growth
- Sporting injuries

Patient factors

Demographic
- Age
- Gender

Knowledge
- Low cancer awareness
- Limited knowledge of complex healthcare systems

Psychological
- Fear
- Growing autonomy
- Confidence in communicating symptoms

Social
- Appearing normal
- Exchanging information with peers
- Accessing information from internet: provides privacy; accessible; creates community
- Influence of parents as reassurance of mediators or referral
- Competing life events

Healthcare factors

System
- Point of first contact GP vs A&E
- Primary physician
- Complex healthcare systems
- Insurance

Healthcare provider and interactions with AYA
- Age of patient
- Socioeconomic status of patient
- Perception of symptoms
- Previous experience of cancer in AYA
- Consultation time
- Continuity in care
- Communication with AYA
- Relationship between AYA-GP
- Previous consultations: not been taking seriously; issues not being addressed; reassurance from GP

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Table 1 Why timeliness to diagnosis remains a top priority

Statement	Source	Level of evidence
Timeliness, 'delay' in diagnosis is frequently a theme in the lay press.	http://www.itv.com/news/2015-06-16/young-patients-facing-significant-delay-in-bowel-cancer-diagnosis/)	+
Relationship of lack timeliness/ delay to poorer outcomes in lay press and research	http://www.clicsargent.org.uk/content/jess-story)	+
A timely diagnosis is a key research priority for young people.	Fern et al 2009 (19), 2013 (13)	+++
Young people are often unaware of the more common cancers that affect their age group.	Hubbard et al 2016 (30)	++
Many young people consult their General Practitioner about their symptoms a number of times.	Gibson et al 2013 (65)	
Low awareness of cancer among primary-care personnel has been described.	http://www.mirror.co.uk/news/uk-news/gps-missing-cancer-children-because-6358489	+
	http://www.clicsargent.org.uk/news/12-04-2016-day-action-tackle-delayed-diagnosis-young-cancer-patients	++

Level of evidence

+ lay press

++ charity report

+++ peer reviewed

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Table 2. Publications outputs from the scoping review

Authors	Year	Country	Patients (N, age range)	Cancer Type	Method	Delay Diagnosis: Influencing Factors
Albriton & Bleyer	2003	UK	N/A	N/A	Review	N/A
Cronholm et al.	2009	USA	N=205 9th and 10th grade males	Testicular cancer	Survey	Knowledge and attitudes towards testicular cancer and testicular self-exam
Dang-Tan & Franco	2007	-	Review of 23 studies (Patients' age range=0-29 years)	N/A	Literature Review	Age Parent level of education Type, site and stage of cancer Presentation of symptoms First medical specialty consulted
Dang-Tan et al.	2008	Canada	N=2,896 Age: 0-19 years	Leukemia; CNS; Lymphoma; Neuroblastoma; Retinoblastoma; Ranal Tumour; Hepatic Tumour; Bone Tumour; Sarcoma; Germ Cell neoplasm; Carcinoma; Other neoplasm	Retrospective review (1995-2000)	Age; cancer type; geographical regions Referral delay
Dang-Tan et al.	2010	Canada	N= 963 leukaemia and 397 lymphoma Age: <19-years	Leukaemia and Lymphoma	A prospective cohort study	Age professional delay (GP vs. A&E) cancer type
Fern et al.	2013	UK	N/A	N/A	Editorial	Age, cancer awareness
Ferrari et al.	2010	Italy	N=575 Age: ≤21 years of age	Soft Tissue Sarcomas (STSs)	Retrospective study (1977-2005)	Patient's age; tumour's site, size, and histological subtype
Gibson et al.	2013	UK	N=24 Age: 16-25	Metastatic adenocarcinoma of the bowel, Osteosarcoma, 2B Hodgkin's lymphoma, 4B Hodgkin's lymphoma, Ovarian dysgerminoma, Ewing's kidney, Synovial sarcoma, ovarian cancer (granulosa cell tumour), B cell lymphoma, Medullablastoma, Osteosarcoma, Neuroblastoma, Ewing's sarcoma, Malignant peripheral nerve sheet tumour	Retrospective (Interviews)	Nature of symptoms – interpreted by young people and others close to them Nature of the relationship with GP Prolonged waiting for appointments, results, referral to a specialist Poor communication between services
Goyal et al.	2004	UK	N=115 Age: 4-22 years	Osteosarcoma and Ewing's sarcoma	Retrospective review (January 1990- April 2002)	tumour's site, size, and histological subtype age professional delay (GP v A&E) access to health professionals
Haim	2004	Israel	N=315 Age: 0-20 years	Solid Tumour (excluding leukaemia)	Retrospective review	Cancer type Age Father's ethnic origin Professional delay (GP v A&E)
Halperin et al.	2001	-	N=122 Age:0 - ≥17	Medulloblastoma	Retrospective review (January 1974- October 1999)	tumour's stage; gender

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Authors	Year	Country	Patients (N, age range)	Cancer Type	Method	Delay Diagnosis: Influencing Factors
Hubbard et al.	2016	UK	N=20173 Mean Age=12.4 (SD=55)	N/A	Cluster randomised controlled trial	Cancer awareness, help-seeking barriers endorsed and cancer communication
Jin et al.	2016	Korea	N= 592 Age:0-18	Acute Lymphoid Leukemia; Acute Myeloid Leukemia; Non-Hodgkin Lymphoma; Central Nervous System tumors; Sarcomas; Neuroblastomas; and Wilms tumor	Retrospective review (2000-2007)	Patient delay (first symptoms/signs of disease and date medical help was first sought); symptom interval (first symptoms/signs of disease and date of diagnosis); patient delay proportion (Patient Delay divided by Symptom Interval); age
Klein-Geltink et al.	2005	Canada	N= 204 Age=15-19years	Leukaemia; Lymphomas; CNS; Bone; Soft tissue; Germ cell ;Carcinoma; Other (hepatic tumours, renal tumours, sympathetic nervous system tumours, and other and unspecified malignant neoplasms)	Retrospective review (1995-2000)	Age Paediatric versus adult oncology treatment centres Referral delay (time between first health-care contact and assessment by a treating oncologist or surgeon)
Kyle et al.	2012	UK	N=478 Age=11-17	N/A	Survey	Cancer awareness
Lethaby et al.	2013		N/A	N/A	Rapid Review	Type of cancer, age
Loh et al.	2012	Singapore	N=390 Age: 0-18	Solid Tumours	Retrospective review (1997-2007)	Age; site of presentation; points of first symptom detection; first healthcare contact; first suspicion of malignancy
Lyratzopoulos et al.	2012	UK	N=41299 Age: 16-85+	Multiple Myeloma, Pacreatic, Stomach, Lung, Hodgkin's Lymphoma, Colon, Ovary, Brain, Non-Hodgkin's Lymphoma, Mesothelioma, Rectal, Renal, Laryngeal, Oesophageal, Leukaemia, Prostate, Vulvar, Cervical, Bladder, Thyroid, Endometrical, Testicular, Melanoma, Breast	Survey	Type of cancer, age, gender
Magni et al	2016	Italy	N=500 Age:15-19	N/A	Survey	Health perception, understanding of oncological disease, reaction to early signs and symptoms potentially attributable to cancer
Martin et al.	2007	USA	N=235 Age: 15–29 years	Leukaemia, Hodgkin's and non-Hodgkin's lymphoma, sarcoma, brain tumours, thyroid cancer	Retrospective review (June 2001-June 2003)	Type of cancer; health insurance
Primeau et al.	2013	USA	N = 1,481 Age: ≥ 18	Breast and cervical cancer	Secondary analysis of the intervention arm of the Boston Patient Navigation Research Program (PNRP)	Social service barriers, site of care, age, race/ethnicity, primary language, and insurance

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Authors	Year	Country	Patients (N, age range)	Cancer Type	Method	Delay Diagnosis: Influencing Factors
Redaniel et al.	2015	UK	N=22,051 Age >15	Breast, colorectal, lung and prostate cancers	Retrospective review (1998-2009)	Presenting symptoms (NICE-qualifying alert symptoms v non-alert symptoms); cancer site, tumour biology and clinical practice
Saha et al.	1993	UK	N=184 Age: 0-15 years	Acute leukaemia; brain tumour; bone tumour; lymphoma; neuroblastoma; rhabdomyosarcoma; nephroblastoma	Retrospective review (January 1982-December 1990)	Age; diagnostic group; geographical factors
Shay et al.	2012	Israel	N=330 Age: 0–18 years	Brain Tumours	Retrospective review Family interview	Delay in indicated imaging; Classic symptoms with a wrong diagnosis; Wrong imaging referral; Administrative delay; family; Wrong interpretation of imaging; Professional delay (GP vs. A&E)
Smith et al.	2007	UK	N=350	N/A	Conference survey	N/A
Stefan & Siemonsma	2011	South Africa	N= 194 children Age: 0-15 years	Lymphoma, Leukaemia, Blastoma, Sarcoma, Brain tumour, Teratoma, Hysticocytosis, other tumours (i.e., less common)	Combined prospective and retrospective study (January 2000- July 2009)	Initial misdiagnoses delay in performing tests and waiting for a histopathology results
Veneroni et al.	2012	Italy	N=425 Age: 28% of them adolescents	Solid Tumours	A prospective series	Age Patient delay (time to first doctor appointment) Referral delay (time taken by the physician to the patient to a specialist - oncologist or surgeon)
Yang et al.	2009	China	N = 51 Age: <18 years	Osteosarcoma	Retrospective study (March 1994-October 2005)	First medical speciality consulted Preceding trauma or sports injury Misdiagnosis

Table 3 Examples of possible future interventional research

Time interval	Recommendation
Appraisal	Target public awareness campaigns. Increase health knowledge and health education in schools. Raise awareness of the more common cancers that occur in this age group. Inform healthcare professionals and health systems of common delays.
Help-seeking	Increase the public's confidence that cancer is a survivable disease. Increase the quality of information available on the Internet. Develop and test strategies that help young people make the most of encounters with primary care. Improve access to primary care - getting appointments, length of appointments and consistency in healthcare professional on each occasion.
Diagnostic	Increase education and training in primary care. Involve young people in the design and review of existing services. Develop strategies to investigate earlier persistent symptoms of common illnesses. Patient as expert needs to be emphasised. Ensure rare cancers are managed in centres of excellence.
Pre-treatment	Explore pre-diagnostic experiences to establish trusting relationships with professionals and services. Offer choice of treatment location where possible. Encourage awareness and services that allow young people to remain in control once a diagnosis is made. Explore communication pathways and blocks between settings and departments of care.