



UNIVERSITY OF LEEDS

This is a repository copy of *Pathways to Diagnosis for Teenagers and Young Adults with Cancer in European Nations: A Pilot Study*.

White Rose Research Online URL for this paper:  
<http://eprints.whiterose.ac.uk/134133/>

Version: Accepted Version

---

**Article:**

Smith, L [orcid.org/0000-0002-4280-6323](https://orcid.org/0000-0002-4280-6323), Pini, S, Ferrari, A et al. (9 more authors) (2018) Pathways to Diagnosis for Teenagers and Young Adults with Cancer in European Nations: A Pilot Study. *Journal of Adolescent and Young Adult Oncology*, 7 (5). pp. 604-611. ISSN 2156-5333

<https://doi.org/10.1089/jayao.2018.0045>

---

© 2018, Mary Ann Liebert, Inc. Final publication is available from Mary Ann Liebert, Inc., publishers <https://doi.org/10.1089/jayao.2018.0045>. Uploaded in accordance with the publisher's self-archiving policy.

**Reuse**

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

**Title:** Pathways to diagnosis for Teenagers and Young Adults with cancer in European nations – a pilot study

**Authors:** Lesley Smith<sup>1</sup>, Simon Pini<sup>2</sup>, Andrea Ferrari<sup>3</sup>, Daniel Yeomanson<sup>4</sup>, Rachael Hough<sup>5</sup>, Pia Riis Olsen<sup>6</sup>, Leila Gofti-Laroche<sup>7</sup>, Thomas Fleming<sup>1</sup>, Martin Elliott<sup>8</sup>, Richard Feltbower<sup>1</sup>, Gabriella Kertesz<sup>8</sup>, Dan Stark<sup>9\*</sup>

#### Affiliations

1. Clinical and Population Science Department, Leeds Institute for Data Analytics, School of Medicine, University of Leeds, Leeds, UK

2. Patient Centred Outcomes Research Group, Bexley Wing, St James's University Hospital and University of Leeds, LS97TF, U.K.

3. Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy, Via G.Venezian, 1 – 20133 – Milan – Italy

4. Sheffield Children's Hospital, Western Bank, Sheffield, S10 2TH

5. University College Hospitals NHS Foundation Trust, Department of Adolescent Haematology, 6th Floor Central, 250 Euston Road, London, NW1 2PG

6. Department of Oncology, Aarhus University Hospital, Nørrebrogade 44, 8000 Aarhus C, Denmark

7. Univ. Grenoble Alpes, Teenagers and Young Adults with Cancer Team  
CHU Grenoble Alpes, 38000 Grenoble, France

8. 2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary

9. Teenage and Young Adult Cancer Services, Institute of Oncology, Leeds Teaching Hospitals NHS Trust. \* corresponding Author d.p.stark@leeds.ac.uk

Acknowledgements: Information described in this article has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under the project ENCCA, grant agreement HEALTH-F2-2011-261474.

## Abstract

### Purpose

The diagnosis of cancer is often prolonged in teenagers and young adults (TYA). There may be lessons in improving this from international comparisons. However, international studies are complex and so we conducted a pilot study to examine the key barriers to large-scale research in this field.

### Methods

We provided translated questionnaires covering key aspects of presentation and clinical management within 60 days of a confirmed cancer diagnosis, to patients aged 13-29 years inclusive, to their primary care physicians and to the cancer specialists managing their cancer. We conducted descriptive analyses of the data and also the process of study implementation.

### Results

For our pilot, collecting triangulated data was feasible but varying regulatory requirements and professional willingness to contribute data were key barriers. The time of data collection and the method for collecting symptom reports were important for timely and accurate data synthesis. Patients reported more symptoms than professionals recorded. We observed substantial variation in pathways to cancer diagnosis to explore definitively in future studies.

### Conclusion

Focussed research upon the mechanisms underpinning complex cancer pathways, and focussing that research upon specific cancer types within TYA may be the key next areas of study.

## Background

Cancer is a substantial cause of morbidity and mortality in teenagers and young adults (TYA) [1, 2]. The incidence in Europe over the last decade is approximately 20 and 28 per 100,000 person years for 15-19 and 20-24 year olds respectively [3] [4],[5]. European data show an annual average incidence increase of 1.5-2.0% [6-9]. TYA with many cancers have poorer outcomes compared to younger children and several have poorer outcomes than older adults [10-13]. European survival rates after TYA cancers vary by geographical region, age group, gender, and cancer type [14, 15].

There is low awareness of cancer during adolescence and early adulthood, in the public and providers and healthcare professionals may not immediately recognise TYA cancer symptoms [16-19]. Therefore, when TYA develop cancer, they may experience a longer time until diagnosis and treatment than younger children or older adults [20-24]. In general, cancers that are more advanced when commencing treatment have poorer outcomes whether due to requiring more treatment (causing greater late toxicity), or through lower treatment success rates and studying and understanding the time to diagnosis is an important TYA cancer research goal [17, 25]. While some studies show a direct correlation, the relation between symptom interval and outcome is complex with clinical, biological and human factors involved. [20, 23]. [16-19]. Access to primary care maybe relevant and health insurance is sometimes relevant [19, 21, 26]. In a large UK primary care cohort study, in the 3 months before diagnosis 42.9% of TYA with cancer consulted primary care  $\geq 4$  times vs 11.5% in age-matched patients without a cancer diagnosis [27]. Almost twice as many TYA visited their GP more than 3 times before diagnosis of cancer than is observed in older adults (38% versus 20%) [28].

Understanding international variation in time to diagnosis could assist us in improving outcomes; sharing of best practice and adhering to consistent research definitions [29, 30]. Previous and ongoing TYA studies do not allow valid international comparisons or identify where long times to diagnosis may be occurring [17, 31]. The international cancer benchmarking project (ICBP) module 4 examined the route from symptoms to cancer treatment in adults and their clinicians [31-33].

Co-operation over large geographical areas and large datasets are required to reach robust research findings particularly given the relatively rarity of AYA cancers [34]. This requires co-operation, infrastructure and funding. International clinical networks and online data capture may overcome some of these barriers, but introduce others. Within the EU FP7 grant 'European Network for Cancer in Children and Adolescents (ENCCA)', between 2011 and 2016, an international collaborative working group of clinicians, researchers and patients in TYA cancer was initiated. As an initial step to developing formal research proposals, the group developed a pilot study as a test case for future larger scale collaborative research. This was undertaken without study management funding but based upon the co-operation present within the network, to examine if this process could minimise the need for full funding for future studies.

### **Study Objectives**

1. To pilot collaborative working and data collection within the European TYA cancer community
2. To identify and characterise timescales within the diagnostic pathway of cancer in the TYA population
3. To examine the consistency of report of waiting times, by the triangulation of the responses of patients with those of clinicians in different healthcare sectors.

## Methods

Investigators were approached through the ENCCA network of TYA professionals.

### Ethics and regulatory elements

Ethics approval was obtained for the use of shared data collection, security and storage procedures, according to the various local and international regulations. The age range for inclusion in the whole project spanned 13-29 year olds although differed in some locations, so two different consent forms were designed: Those under 16 years required both the consent of a parent/guardian and patient assent, whereas those over 16 years consented directly.

### Eligibility criteria

#### Patients

- Aged between 13 and 29 years on study entry
- Diagnosed with leukaemia, sarcomas of bone or soft tissue, lymphomas, central nervous system tumours, germ cell tumours or carcinoma.
- Was receiving or had received care in a contributing specialist centre.
- Less than 60 days from cancer diagnosis.
- Able to complete the questionnaire, with help from another person if necessary



## Professionals

- The oncology/haematology specialist involved in the care of the patient
- The GP/community/ primary care doctor who initially saw the patient and/or made the referral to specialist services.

These professionals were identified by the patient in their questionnaire.

## Questionnaires

Questionnaires developed in the international cancer benchmarking project module 4 [31, 32] were adapted by experienced cancer clinicians and the research team to better fit the TYA population. The questionnaires contained items related to symptoms, clinical contact/interventions and time periods. Three different versions were developed; for patients, oncology/haematology specialists and general practitioners (GP)/primary care physicians.

## Patient Questionnaire

Each TYA participant was asked for limited demographic and clinical details, but no personally identifiable information was requested (Appendix 1).

When the participant identified their specific diagnosis they then selected from a list of cancer symptoms compiled by experienced clinical study members, tailored to each cancer type and including free space to add other symptoms they experienced before their diagnosis. This aimed to focus upon relevant specific symptoms. The patient was also asked about events leading to diagnosis and to estimate dates of key events in their pathway including dates of first symptoms, referral, diagnosis and treatment.

### Primary Care questionnaire

The primary care clinician's questionnaire documented the symptoms of their patient using free text to encourage wide reporting, as well as how many clinical assessments occurred in primary care. They were asked what investigations were ordered and when/how they referred the patient further. The research team wrote the information sheet to help GPs feel confident in participating, by explaining that that this research was not designed to criticise them or to imply any mistakes or delays, but to understand processes and compare perspectives when measuring previous events (see GP information sheet in Appendix 2).

### Specialist questionnaire

The specialist questionnaire asked consultant oncologist/haematologists questions about how the patient was first referred to their service. They were also asked how the patient was diagnosed and the details of their diagnosis and treatment. Again, the information sheet emphasised there was no criticism or implication of delay. .

### Data collection

A bespoke online system was developed for the data collection in this project, with a unique and secure login system for each participating country that could link patients' data to their GPs and specialists.

The GPs and specialists had the same prefix as their patient, so that the data could be linked e.g. GB0101P would be linked with GB0101G and GB0101C. To access the system each participant was given a login card (see Appendix 1), for secure use on

the survey website to input their patient ID, authentication code and three grid references (e.g. A1, C5, H2). The grid references changed upon website access, enhancing data security.

Development of the website took 5 months including piloting with 2 service users. The questionnaires were translated forwards from English into the different languages appropriate and back-translated to ensure accuracy, co-ordinated by the lead national collaborator.

Each centre could access our survey website to review local progress, and generate local login cards for their participants. A Centre Management Report allowed the local investigator to see when a patient had completed the questionnaire and also to see the details they had provided for their GP and specialist, to invite those professionals to take part.

### **Statistical analysis**

Descriptive statistics were used to assess the questionnaires completed. Where appropriate this included reporting the number of missing responses for each question. Questionnaire responses were compared between pairs of responders (e.g. patient and GP) and agreement assessed by the Kappa statistic.

Time differences in the patient pathway between key events were calculated from the dates provided by the patients. We calculated the difference between 1) first symptoms and GP appointment, 2) first symptoms and appointment with a specialist,

3) first symptoms and cancer diagnosis, 4) GP appointment and appointment with specialists, 5) GP appointment and cancer diagnosis. Patient pathway times were reported by median and interquartile range (IQR)

We compared responses by country for those with the highest number of responders (England, Italy versus Others including France, Denmark and Hungary). Comparison of responses between subgroups (such as age group or tumour type) were not appropriate due to the pilot aims and small sample.

## Results

### Study approval

Initially 7 UK departments expressed interest in the study from 4 treatment centres (Leeds x2, Sheffield x2, Birmingham x2 and London) and 13 EU Centres in 5 countries (Italy, France x5, Spain x5, Hungary and Denmark). Swedish and German centres then could not proceed without funding for ethics and an employee to deliver the project. The timeliness of study opening varied by over 12 months, and it was not always possible to open the study due to available resources (Figure 1).

### Data

A total of 9 centres in 5 countries participated; responses for each are shown in table 1. A total of 68 patients, 42 GPs and 50 specialist centres completed their respective questionnaires. Responses for all three elements (patient, GP and specialist centre) were completed by 32. While the greatest number of patient responses were completed in England, the other countries, in particular Italy, were more successful in obtaining responses for all three responder types.

A wide range of symptoms were reported by patients and GPs, with more symptoms reported by patients (table 2). The most commonly reported symptoms by the patients were: swelling or lump with no pain (31%), bone pain (31%), tiredness (26%), swelling or lump with pain (18%). Swelling or lump with pain was the most commonly reported symptom by the GP (31%) followed by bone pain (24%).

Almost 50% of patients reported seeing their GP between 1 and 4 weeks from first symptoms, and 18% reported waiting more than 1 month with symptoms before contacting a GP. However, 47% of GPs reported that the patients waited more than 1 month with symptoms before contacting them (Table 3). Overall 39% of patients reported visiting their GP twice or more before diagnosis (table 5). This was different between countries; 47% in England, 34% in Italy and 35% in the other countries combined, but not statistically significantly ( $p=0.44$ ). The use of emergency hospital services (accident and emergency departments) was low, and consistent between reporters. Referrals direct to cancer specialist teams were uncommon, being more often into a non-specialist hospital doctor and then onward referral to oncology/haematology.

Within the limitations of our pilot design, we observed shorter median times from symptom onset to specialist appointment and from symptoms to diagnosis in Italy than in the other nations studied and the longest in the UK (see Supplementary table 1).

Triangulating the data, there was inconsistency of reporting of the diagnostic process (table 4). Two thirds of patients reported initially seeing a GP about symptoms and

21% reported attending emergency services. A third of GPs reported making an urgent referral for assessment of cancer, while only 14% of specialist centres reported receiving a referral from a GP.

Patients reported a wide range of times between key points on the patient pathway (figure 3). The median time between patients reporting symptoms and seeing a specialist was 59 days (IQR 31 to 130 days). However, patients were then promptly diagnosed after seeing a specialist with the median time from symptoms to cancer diagnosis 63 days (IQR 35 to 153 days). Where data on time from symptoms to diagnosis were present from several sources (in 18 patients), the reported time differences were modest; mostly under 14 days and never over 30 days. For all time periods there were some patients with extended times on the diagnostic pathway.

## Discussion

In this feasibility pilot study, we have demonstrated that international multi-professional research, including patients as direct data contributors in TYA with cancer, is feasible within our international collaborative network. Conducting such research without grant funding was difficult. Responses from primary care were the most difficult to obtain, but not impossible and not uniformly obtained by country. The results observed for patient experience must be interpreted with caution given our pilot aims and sample size.

There were significant variations and barriers presented by regulatory aspects. Translation of study forms significantly delayed study implementation. Administrative burdens upon the study team and investigators varied across locations within Europe, despite local research teams being highly motivated to participate. Imbalances

between available research resource and local governance requirements resulted in inequity in our ability to open the study in a timely manner, or to open it at all in some places. Explicit unified European positions on these issues for relatively low-risk questionnaire-based studies could substantially improve research productivity. We recommend proportionate review systems for defined low risk projects are considered internationally according to local systems [35].

Although our pilot study had limited sample size, the findings are broadly comparable with other studies. We found approximately 40% of patients visited their GP at least twice prior to diagnosis. In comparison, a large UK primary care cohort study, in the 3 months before diagnosis 42.9% of TYA with cancer consulted primary care  $\geq 4$  times vs 11.5% in age-matched patients without a cancer diagnosis [27]. Almost twice as many TYA visited their GP more than 3 times before diagnosis of cancer than is observed in older adults (38% versus 20%) [28]. We found the median time from reporting symptoms to cancer diagnosis was 9 weeks. In comparison a 2007 study [36] showed a median time from symptom onset to diagnosis of 9.5 weeks (range 2–191.5 weeks). We identified marked differences in the proportion of repeated visits reported by GPs and patients. A survey of 174 TYA patients in 2004 showed that 20% of patients waited several months before seeking help after experiencing symptoms and that 71% of TYAs also reported visiting their GP 2-5 times before being referred to a specialist [37]. Some of the reasons given for this delay included; being scared to seek help, ignoring symptoms, concerned or embarrassed about symptoms, not having time, concerns about not being taken seriously and fear of bad news [36, 37]. Symptoms reported were distinct between primary care and patients, despite data collection being shortly after diagnosis. It is possible primary care recorded only the

most clinically worrying symptom. Pain was a common feature of primary care physicians' reported symptoms, although patients commonly reported painless lumps. The range in times from onset of symptoms to diagnosis in our study are very wide, while the median times are reasonable clinically for the cancers being considered. This asymmetric and skewed distribution may indicate a sporadic not a systematic prolongation of the process. This is reflected in the recent 'three-legged' approach to health service improvement in Denmark [38, 39]. The characteristics and risk factors associated with this could be examined in a larger study, focusing upon the cancers where data most strongly indicates a prolonged pathway is detrimental [40]. In the UK campaigns designed to increase awareness of the signs and symptoms of TYA cancers have been implemented [41].

There are obvious limitations of this study; it was not intended as a comprehensively sampled inception cohort design, included recruitment only at selected centres with small sample size. Eligibility only shortly after diagnosis may have limited recruitment. The study clearly requires extension before firm conclusions can be reached. However, we met our main pilot study objectives; we demonstrated the feasibility of such studies which cross traditional data-reporting approaches, including the collection of triangulated data. There are preliminary signals of possible differences in these patient pathways internationally which merit confirmation as well as exploration of mechanisms in future work. The study also indicated some key methodological learning for more definitive future studies; patients reported a larger burden of symptoms than GPs. However patient's symptoms were reported from a check list, whereas GPs reported symptoms via a free text field, and GP records may well only include key symptoms even when free text is available. The evolution in the perception



of events over time is apparent, with patients reporting primary care consultations at the outset of their pathways but their oncology specialists not identifying this from their records. Precise recording of the relation between the date of events and of data collection may be very important in conducting future larger-scale studies. The proportion reporting a shorter symptom duration was higher for patients than it was by GPs. This may be important when measuring this in future studies. Triangulating the responses from patients, primary care and secondary care clinicians about how symptoms were investigated through health services via various emergency and elective providers requires the development of a clear shared terminology.

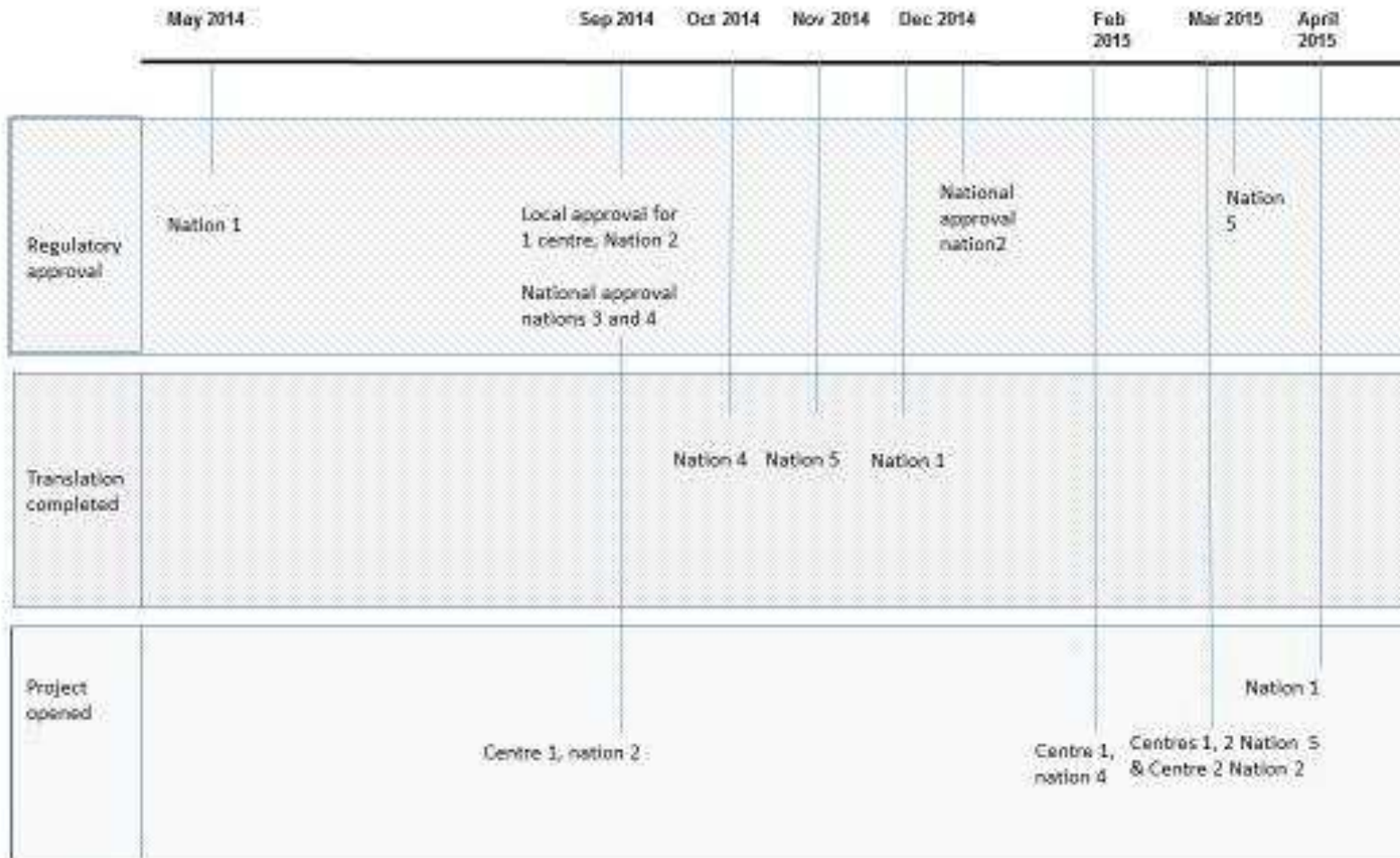
The importance on international networking (as demonstrated by this study) is clear in driving and delivering such a study, and the ability of a network such as ENTYAC to increase our understanding and potentially reduce diagnostic delay is apparent [42]. Our group plan to take this learning forward in building multi-centre European studies for TYA with cancer in this and other areas of enquiry

It is interesting to note from the current literature the influence that the initial clinical impression or extent of 'cancer suspicion' of the initially assessing GP has upon the subsequent pathway. This impression may be due to the presence of non-specific symptoms (such as lump without pain) at that assessment. However, many cancers present without specific symptoms, particularly while of early stage, and this may be unduly influencing clinical behaviour [43]. This is particularly relevant to TYA. As TYA have less experience of medical encounters and greater embarrassment when reporting symptoms, the proportion giving non-specific descriptions may be increased [44, 45]. If this is coupled with a low clinical suspicion (driven by the epidemiology), long delays would then occur for cancers where non-specific symptoms are reported.

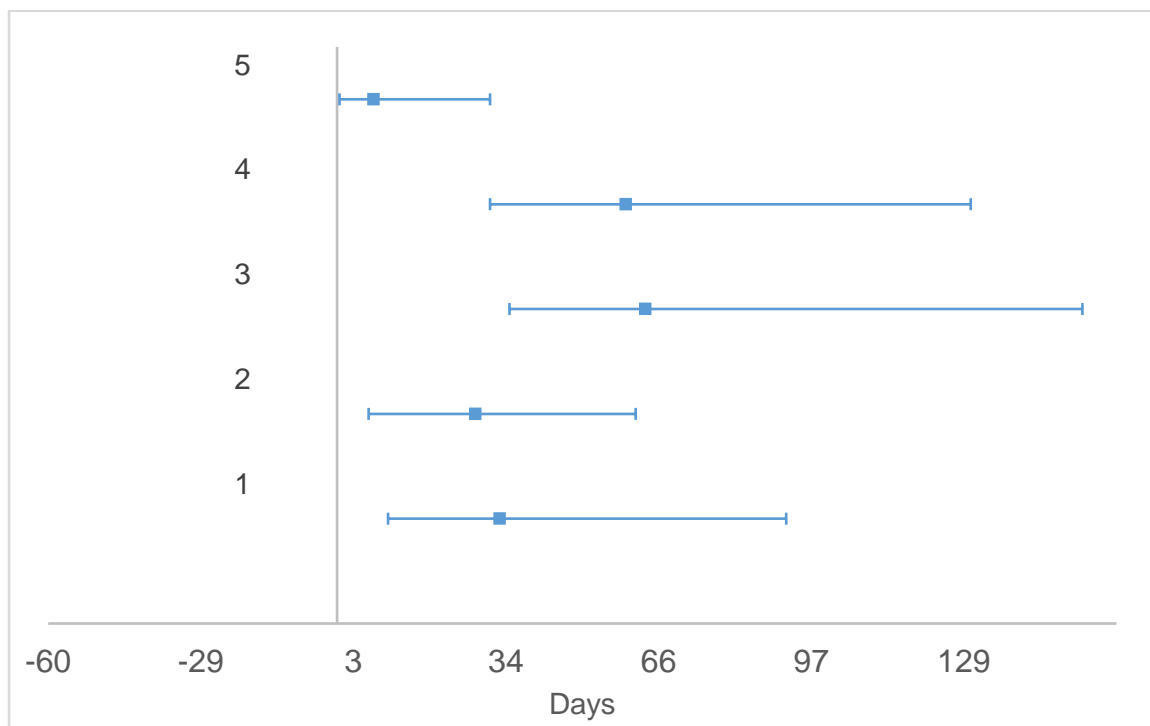
In future we propose to focus upon the experiences of TYA patients with very long times to diagnosis, specifically where time from symptoms to diagnosis appears to markedly influence clinical outcome; non-rhabdomyosarcoma soft tissue sarcoma, and advanced germ cell tumour [41]. Analyses by cancer type were not possible in our sample size, nor appropriate in a pilot design. Very long diagnostic pathways may be clinically important and costly to healthcare resources, but moreover are highly emotive for patients, carers and clinicians, and may promote a clinical impression that all pathways are more prolonged than they generally are.

## Tables and Figures

**Figure 1: A timeline for the opening of the pilot study, in successful and other initially interested centres**



**Figure 2: Patient reported pathway times (median and IQR)**



**Table 1: Responses by country**

Country	No. of centres	Patient responses	GP responses	Centre responses	All responses	3
England	3	30	12	14	4	
France	3	9	7	9	7	
Italy	1	21	16	20	15	
Denmark	1	4	4	4	4	
Hungary	1	4	3	3	2	
<b>Total</b>	<b>9</b>	<b>68</b>	<b>42</b>	<b>50</b>	<b>32</b>	

**Table 2: Patient and GP reported frequent symptoms**

Symptom	Patient (N=68)		GP (N=42)	
	n	%	N	%
Swelling/lump with no pain	21	31	6	14
Bone pain	21	31	10	24
Tiredness	18	26	4	10
Swelling/lump with pain	12	18	13	31
Weight loss	9	13		
Abdominal pain	9	13	2	5
Breathlessness	8	12	1	2
Night sweats	5	7		
Cough	5	7	4	10
Sweats	4	6		
Feeling sick	4	6		
Headaches	4	6	2	5
Poor balance	4	6	3	7
Reduced movement	4	6		
Other*	39	50	11	25

\*Other included: Drowsiness, Enlarged lymph nodes, Uncoordinated walking, Loss of vision or double vision, High temperature, Irregular periods, Itching, Bruising, Enlarged spleen, Fever, Infection, Diarrhoea, Difficulty swallowing, Numbness, Problems with writing or doing calculations, Recurrent infections, Seizures, Broken bones, Changes in personality and intellect, Vomiting, Weight gain

**Table 3: Symptom duration (time from first symptoms to contacting GP), patient and GP reported**

Symptom duration	Patient (N=68)		GP (N=42)	
	n	%	n	%
Less than 1 week	14	21	3	7
1-4 weeks	33	48	16	38
5-7 weeks	3	4	6	14
2-5 months	5	7	9	21
6-12 months	3	4	3	7
More than 12 months	2	3	2	5
N/A or no symptoms (e.g. screen detected)	5	7	3	7
Missing	3	4		

35 with both patient and GP reported duration: Kappa agreement = 46% (moderate agreement)



**Table 4: Pathway and referral process, patient, GP and centre reported outcomes**

	n	%
<b>Patient response†</b>	N=68	
I had symptoms/I noticed a bodily change and went to see a doctor (GP)	41	60
I had symptoms/I noticed a bodily change as went/was taken to Accident and Emergency (A&E)	6	9
I had seen a doctor/GP with symptoms, but went/was taken to A&E when things worsened	8	12
I was being investigated by my doctor for another problem during which time the cancer was discovered	7	10
Other	2	3
Missing	4	6
<b>GP responses ††</b>	N=42	
Emergency admission: a referral to A&E for immediate admission	6	14
An urgent referral for assessment of cancer symptoms/signs/test results	14	33
A less urgent referral in which cancer is raised as a possibility	2	5

A more general referral for investigation and assessment without cancer mentioned	7	17
No referral was made	4	10
Other	5	12
Missing	4	10
<hr/>		
<b>Centre responses †††</b>	N=50	
GP referral	7	14
Medical specialist/consultant referral;	23	46
Referral from another hospital outpatient clinic	12	24
Other	7	14
Missing	1	2
<hr/>		

†Patient question: Which of the following best describes the events which led to your diagnosis of cancer?

††GP question: If you made a referral to specialist services, which of the following best describes the nature of this referral?

†††Centre question: How was the patient referred to the hospital/specialist services related to their cancer?

**Table 5: Number of times contacted GP before diagnosis, patient reported response overall and by country**

	All (N=68)		England (n=30)		Italy (n=21)		Other (n=17)†	
	n	%	n	%	n	%	n	%
0	8	12	3	10	2	10	3	18
1	25	37	7	23	10	48	8	47
2-3	22	32	11	37	6	29	5	29
4+	5	7	3	10	1	5	1	6
Missing	8	12	6	20	2	10		

† Other includes Denmark, France and Hungary

## References

1. Lewis, I.J., *Cancer in adolescence*. Br Med Bull, 1996. **52**(4): p. 887-97.
2. Stark, D. and I. Lewis, *Improving outcomes for teenagers and young adults (TYA) with cancer*. Klin Padiatr, 2013. **225**(6): p. 331-4.
3. Brierley, R., Holmes, D., Ceschia, A., Jouret, J., *Teenage Cancer Trust: pursuing equality*. Lancet Oncology, 2009. **10**(5): p. 455-8.
4. Gatta, G., et al., *Survival of European children and young adults with cancer diagnosed 1995-2002*. Eur J Cancer, 2009. **45**(6): p. 992-1005.
5. Trama, A., et al., *Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EURO CARE-5*. Lancet Oncol, 2016. **17**(7): p. 896-906.
6. Aben, K.K., et al., *Cancer in adolescents and young adults (15-29 years): a population-based study in the Netherlands 1989-2009*. Acta Oncol, 2012. **51**(7): p. 922-33.
7. Desandes, E. and D.P. Stark, *Epidemiology of Adolescents and Young Adults with Cancer in Europe*. Prog Tumor Res, 2016. **43:1-15**.(doi): p. 10.1159/000447037. Epub 2016 Sep 5.
8. O'Hara, C., et al., *Trends in survival for teenagers and young adults with cancer in the UK 1992-2006*. Eur J Cancer, 2015.
9. Stark, D., et al., *Survival patterns in teenagers and young adults with cancer in the United Kingdom: Comparisons with younger and older age groups*. Eur J Cancer, 2015.
10. Bielack, S.S., et al., *Bone tumors in adolescents and young adults*. Curr Treat Options Oncol, 2008. **9**(1): p. 67-80.
11. Bleyer, A., et al., *Relative lack of conditional survival improvement in young adults with cancer*. Semin Oncol, 2009. **36**(5): p. 460-7.
12. CRUK. *Teenage and young adult cancer statistics*. 2013 13-05-2013].
13. Ferrari, A., et al., *Starting an adolescent and young adult program: some success stories and some obstacles to overcome*. J Clin Oncol, 2010. **28**(32): p. 4850-7.
14. Birch, J.M., et al., *Survival from cancer in teenagers and young adults in England, 1979-2003*. Br J Cancer, 2008. **99**(5): p. 830-5.
15. De Angelis, R., et al., *Cancer survival in Europe 1999–2007 by country and age: results of EURO CARE-5—a population-based study*. The lancet oncology, 2014. **15**(1): p. 23-34.
16. Bleyer, A. and R. Barr, *Cancer in young adults 20 to 39 years of age: overview*. Semin Oncol, 2009. **36**(3): p. 194-206.
17. Albritton, K.H. and T. Eden, *Access to care*. Pediatric blood & cancer, 2008. **50**(S5): p. 1094-1098.
18. Dang-Tan, T. and E.L. Franco, *Diagnosis delays in childhood cancer*. Cancer, 2007. **110**(4): p. 703-713.
19. Fern, L.A., et al., *How frequently do young people with potential cancer symptoms present in primary care? British Journal of General Practice*, 2011. **61**(586): p. e223-e230.
20. Goyal, S., et al., *Symptom interval in young people with bone cancer*. Eur J Cancer, 2004. **40**(15): p. 2280-6.
21. Martin, S., et al., *Delays in cancer diagnosis in underinsured young adults and older adolescents*. Oncologist, 2007. **12**(7): p. 816-24.
22. Desandes, E., et al., *Pathways of care for adolescent patients with cancer in France from 2006 to 2007*. Pediatr Blood Cancer, 2012. **58**(6): p. 924-9.
23. Veneroni, L., et al., *Symptom interval in pediatric patients with solid tumors: adolescents are at greater risk of late diagnosis*. Pediatr Blood Cancer, 2013. **60**(4): p. 605-10.
24. Klein-Geltink, J., et al., *Impact of age and diagnosis on waiting times between important healthcare events among children 0 to 19 years cared for in pediatric units: the Canadian Childhood Cancer Surveillance and Control Program*. Journal of pediatric hematology/oncology, 2006. **28**(7): p. 433-439.

25. Coccia, P.F., et al., *Adolescent and Young Adult Oncology, Version 2.2018*, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw., 2018. **16**(1): p. 66-97. doi: 10.6004/jnccn.2018.0001.
26. Bleyer, A., *The adolescent and young adult gap in cancer care and outcome*. Curr Probl Pediatr Adolesc Health Care, 2005. **35**(5): p. 182-217.
27. Dommett, R., et al., *Features of cancer in teenagers and young adults in primary care: a population-based nested case-control study*. Br J Cancer, 2013. **108**(11): p. 2329-2333.
28. Furness, C.L., et al., *Cancer Patient Experience in the Teenage Young Adult Population- Key Issues and Trends Over Time: An Analysis of the United Kingdom National Cancer Patient Experience Surveys 2010-2014*. J Adolesc Young Adult Oncol., 2017. **6**(3): p. 450-458. doi: 10.1089/jayao.2016.0058. Epub 2017 May 19.
29. Lethaby, C.D., et al., *A systematic review of time to diagnosis in children and young adults with cancer*. Arch Dis Child., 2013. **98**(5): p. 349-55. doi: 10.1136/archdischild-2012-303034. Epub 2013 Mar 9.
30. Launay, E., et al., *Inadequate critical appraisal of studies in systematic reviews of time to diagnosis*. J Clin Epidemiol., 2016. **78**:43-51.(doi): p. 10.1016/j.jclinepi.2016.03.013. Epub 2016 Mar 30.
31. Weller, D., et al., *The Aarhus statement: improving design and reporting of studies on early cancer diagnosis*. Br J Cancer, 2012. **106**(7): p. 1262-1267.
32. Coleman, M.P., et al., *Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data*. Lancet, 2011. **377**(9760): p. 127-38.
33. Weller, D., et al., *An investigation of routes to cancer diagnosis in 10 international jurisdictions, as part of the International Cancer Benchmarking Partnership: survey development and implementation*. BMJ Open., 2016. **6**(7): p. e009641. doi: 10.1136/bmjopen-2015-009641.
34. Gatta, G., et al., *Rare cancers are not so rare: the rare cancer burden in Europe*. Eur J Cancer., 2011. **47**(17): p. 2493-511. doi: 10.1016/j.ejca.2011.08.008. Epub 2011 Oct 25.
35. NHS Health Research Authority. *Proportionate Review Information and Guidance for Applicants*. <https://www.hra.nhs.uk/documents/1022/proportionate-review-information-guidance-document.pdf>. 2018 [Accessed 15th May 2018].
36. Eden, T., et al. *Symptom interval (SI) in teenagers and young adults (TYA) with cancer*. in *Pediatric blood & cancer*. 2007. WILEY-LISS DIV JOHN WILEY & SONS INC, 111 RIVER ST, HOBOKEN, NJ 07030 USA.
37. Smith, S., et al., *The experiences of teenagers and young adults with cancer—results of 2004 conference survey*. European Journal of Oncology Nursing, 2007. **11**(4): p. 362-368.
38. Jensen, H., M.L. Topping, and P. Vedsted, *Prognostic consequences of implementing cancer patient pathways in Denmark: a comparative cohort study of symptomatic cancer patients in primary care*. BMC Cancer., 2017. **17**(1): p. 627. doi: 10.1186/s12885-017-3623-8.
39. Vedsted, P. and F. Olesen, *A differentiated approach to referrals from general practice to support early cancer diagnosis - the Danish three-legged strategy*. Br J Cancer., 2015. **112**(Suppl 1): p. S65-9. doi: 10.1038/bjc.2015.44.
40. Ferrari, A., et al., *The Sooner the Better? How Symptom Interval Correlates With Outcome in Children and Adolescents With Solid Tumors: Regression Tree Analysis of the Findings of a Prospective Study*. Pediatric Blood & Cancer, 2016. **63**(3): p. 479-85.
41. Kyle, R.G., et al., *Increased cancer awareness among British adolescents after a school-based educational intervention: a controlled before-and-after study with 6-month follow-up*. BMC Public Health, 2013. **13**(1): p. 190.
42. Stark, D., et al., *Teenagers and young adults with cancer in Europe: from national programmes to a European integrated coordinated project*. Eur J Cancer Care (Engl), 2015.

43. Jensen, H., et al., *Cancer suspicion in general practice, urgent referral and time to diagnosis: a population-based GP survey and registry study*. BMC Cancer, 2014. **14**: p. 636.
44. Fern, L.A., et al., *Why can't we improve the timeliness of cancer diagnosis in children, teenagers, and young adults?* BMJ, 2013. **347**: p. f6493.
45. Fern, L.A., et al., *How frequently do young people with potential cancer symptoms present in primary care?* Br J Gen Pract, 2011. **61**(586): p. e223-30.

