EJC Paediatric Oncology 4 (2024) 100191

Contents lists available at ScienceDirect

EJC Paediatric Oncology

journal homepage: www.journals.elsevier.com/ejc-paediatric-oncology

A review calling for research directed at early detection of childhood cancers: The clinical, scientific, and economic arguments for population screening and surveillance

John Apps [a,1], Timothy A. Ritzmann [e,m,1], JoFen Liu [e,m], Dhurgshaarna Shanmugavadivel [e,m], Christina Halsey [b], Kathy Pritchard Jones [c], Rifat Atun [d], Kathy Oliver [f], Kavita Vedhara [g], Ashley Ball-Gamble [h], Neil Ranasinghe [i], Angela Polanco [j], Jenny Adamski [k], Adam L. Green [l], David A. Walker [e,m,*]

[a] University of Birmingham, UK
[b] University of Glasgow, UK
[c] University College London, UK
[d] Harvard University, USA
[e] School of Medicine, University of Nottingham, UK
[f] International Brain Tumor Alliance (IBTA), UK
[g] Centre for Academic Primary Care, University of Nottingham, UK
[h] Children's Cancer & Leukaemia Group, Leicester, UK
[i] Parent advocate, UK
[j] National Co-Ordinating Centre, Cancer Research Network, UK
[k] Birmingham Children's Hospital, UK
[l] Children's Hospital Colorado, USA
[m] Children's Brain Tumour Research Centre, University of Nottingham, UK

ARTICLE INFO

Keywords:
Accelerating cancer diagnosis
Newborn screening
Child health surveillance
Cancer predisposition
Childhood mortality
Childhood disability
Health economics

ABSTRACT

Childhood cancers are increasingly recognised as disorders of tissue growth and development, through early life into adulthood. A rising proportion are currently considered to be related to a familial predisposition or associated with identified genetic mutations in predisposition genes. Their threat to life and risk of associated serious disability at diagnosis and need for complex life saving therapies makes them a research priority. Inadequate progress has been made in diagnosing childhood cancers earlier within global health systems, which means that their clinical presentations are either missed altogether or constitute high risk emergencies. Whilst knowledge of tumour biology has improved dramatically over the last decade due to the expansion in research technologies directed at innovative approaches to prognostication and treatment. A concerted research initiative to apply this knowledge to making the diagnosis of childhood cancers at earlier points in tumourgenesis has not developed. The risk for a child getting a cancer by the age of 5 is equivalent to the risks of the conditions selected as part of newborn population screening for rare inherited health conditions and is nearly 3 times that at age 18 years. We are proposing that research directed at accelerating cancer diagnosis for children by focussing upon feasibility and acceptability of linking targeted surveillance with population screening for all childhood cancers. This would be supported by enhanced public and professional awareness of a child's risks of cancer and the range of clinical presentations. We suggest this must now be a top priority for research because of the potential for improving outcomes for treatment of all types of cancer and reducing the burden of disability and late effects of therapy.

* Correspondence to: Emeritus Professor Paediatric Oncology, School of Medicine, University of Nottingham, Queen's Medical Centre, Nottingham NG7 2UH, UK.
E-mail address: David.walker@nottingham.ac.uk (D.A. Walker).
[1] Joint first authors.

https://doi.org/10.1016/j.ejcped.2024.100191
Received 10 October 2023; Received in revised form 21 August 2024; Accepted 5 September 2024
Available online 26 September 2024

1. Introduction

In recent years, research into early detection and prevention of adult cancer has rapidly expanded, seeking ways to anticipate the clinical presentation of cancer in order to offer earlier intervention and improve outcomes [1–3]. This strategy is justified by the high lifelong risk of cancer development, the recognition that many cancers have a prolonged pre-diagnostic interval measured in years or decades, the adverse consequences on outcomes associated with prolonged diagnostic intervals [4] and the expansion of improved and increasingly targeted treatments [5]. There are also powerful arguments that early detection and prevention are vitally important in childhood cancer ***(text box 1)***.

Despite these benefits, proposing a similar approach in childhood

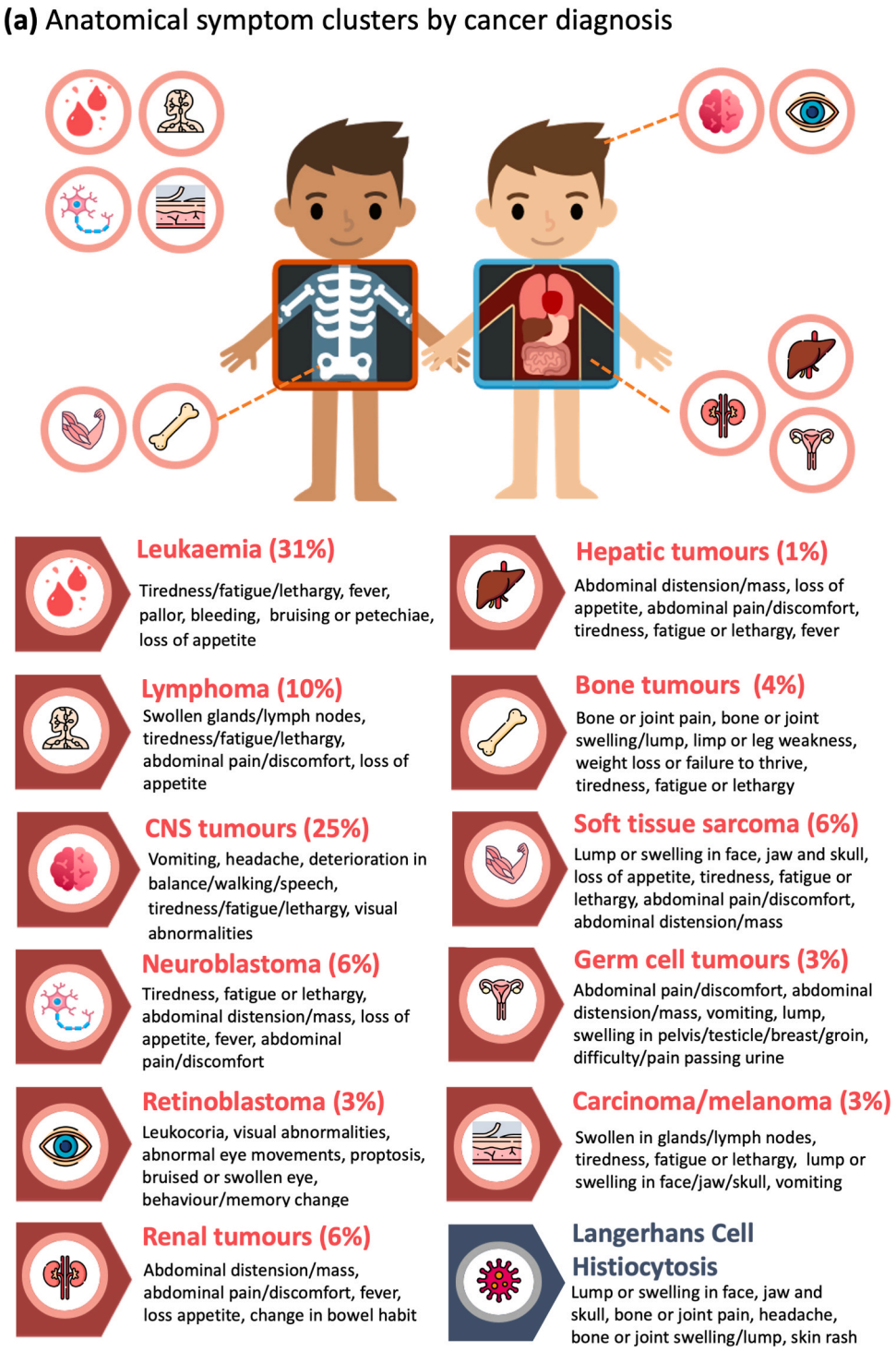

Fig. 1. a: This figure shows the population proportion, anatomical distribution and ranked symptom clusters for eleven recognised child cancer groups from the ICD -O (excluding miscellaneous) and Langerhans Cell Histiocytosis. (https://seer.cancer.gov/iccc/iccc3.html). Fig. 1b: This figures shows the correlation between host tissue growth rates in childhood and age incidence of childhood cancers supporting the hypothesis that tissue growth rates interact with age related risks of cancer presentation. [13,14]. Fig. 1c: This compares the population age incidence of cancer during childhood to population incidence of "screened-for" inherited conditions [15].

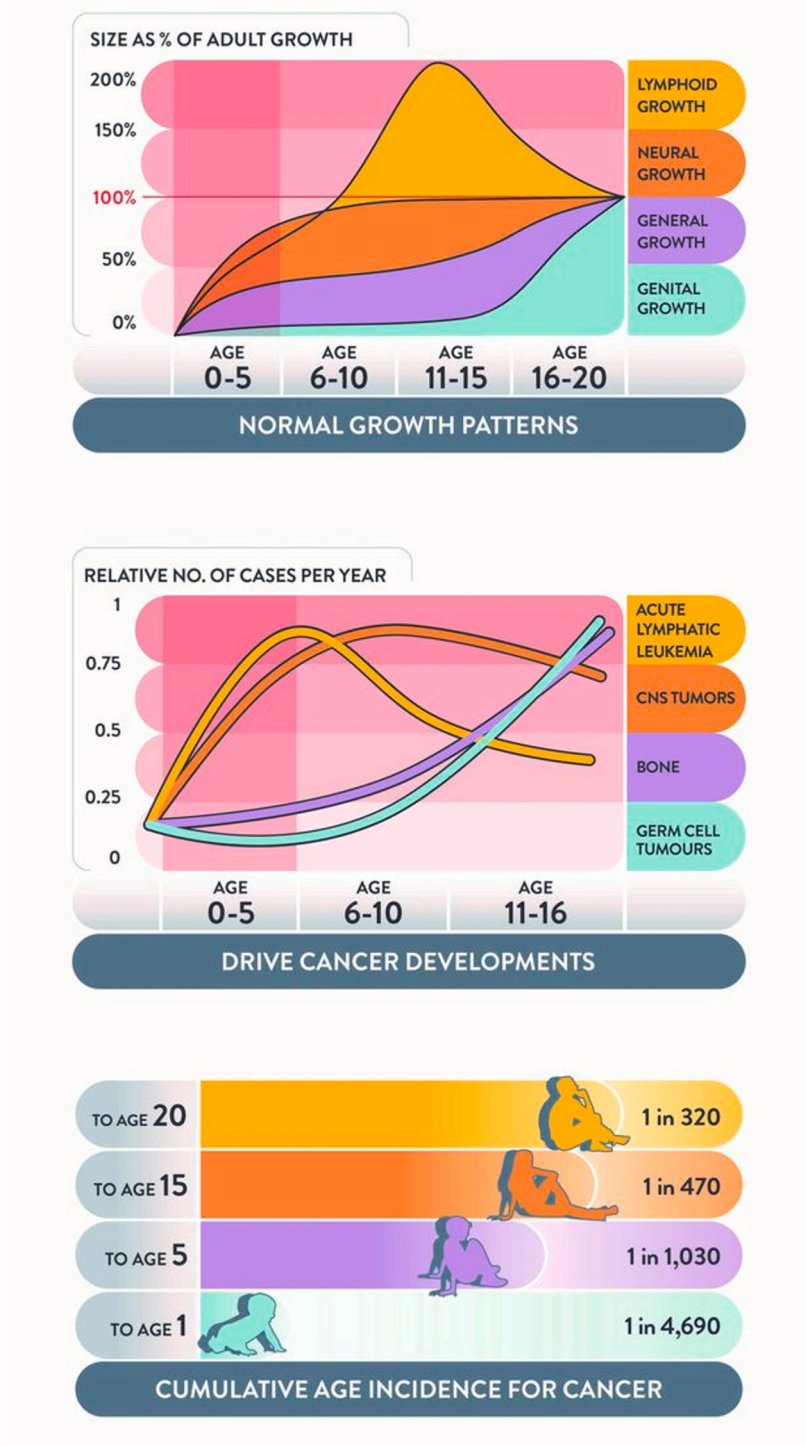

Fig. 1. (*continued*).

cancer has been constrained by a number of arguments that raise concerns for policymakers. They include: 1) childhood cancers are too rare to justify screening; 2) the pre-diagnostic period for childhood cancer is too short; 3) surveillance and screening for childhood cancer will not lead to better outcomes; 4) the risks of screening are unacceptable to families and healthcare professionals, and 5) screening for cancer in childhood is not economically justified [6–8]

As a consequence of dialogue between childhood cancer research clinicians and specialist patient advocates, we aim to present arguments to justify a reappraisal of these attitudes. By addressing each of these concerns in turn we will identify key areas requiring further research and investment to offer the possibility that childhood cancers are not left behind in the early cancer detection and prevention revolution.

2. Are childhood cancers too rare to justify screening?

The summary infographic (Fig. 1a,b &c) identifies the childhood cancer groups, their anatomical distribution and symptom clusters

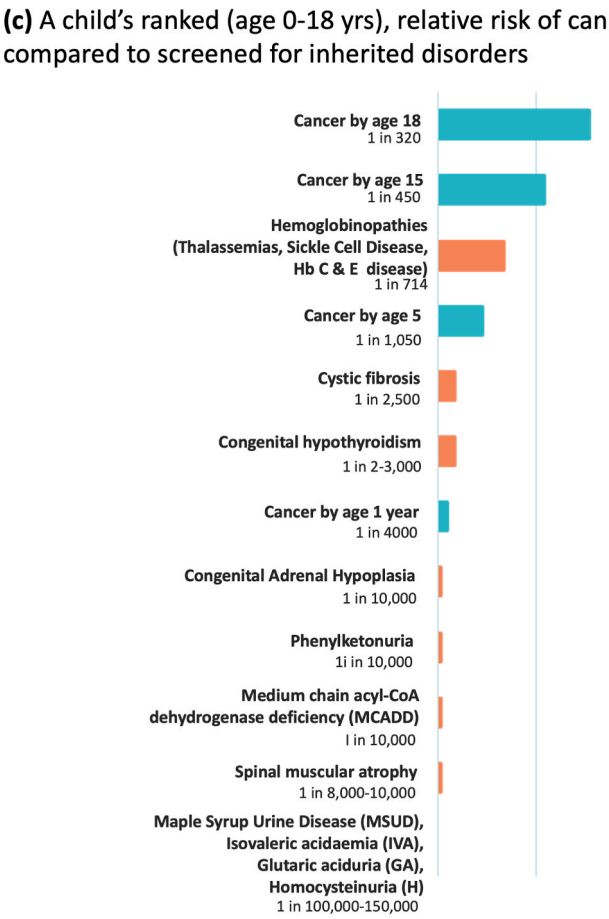

Fig. 1. (*continued*).

(Fig. 1a), the correlation with tissue growth patterns and age-incidence patterns of cancer types and age incidence of cancer risk across childhood (Fig. 1b), and the relative risk of age-related cancer incidence with the population incidence of "screened-for inherited health conditions (Fig. 1c). Without treatment, all childhood cancers are associated with a short life expectancy, distressing symptomatology and the high risk of progressive disability leading to great distress for the child and family [9]. Currently treatments in high income countries offer > 80 % lifelong cure rates with timely diagnosis and intensive treatments. Prognosis in low and middle income countries differ markedly, determined by a wide range of cultural, political and health system factors [10]. It is notable that a child's risk of cancer is relatively consistent, globally [11]. Selection of a suitable screening method is not without risk as it must be acknowledged that there are marked differences in penetrance of diagnostic markers for inherited genetic /metabolic conditions and penetrance of genetic markers of cancer susceptibility genes in affected individuals, which are lower still for individuals with pathogenic/likely pathogenic (P/LP) variations. Furthermore, the timing of predictive biosamples for genetic / metabolic conditions are reliable at birth but for childhood cancers are largely unexplored [12].

3. Is the pre-diagnostic period too short?

The genetic and developmental origins of childhood cancers diverge from their adult counterparts. Most tumours in adults result from the cumulative acquisition of mutations associated with ageing, coupled with lifestyle factors over decades of life. Childhood cancers are not generally considered a product of preventable, postnatal, environmental factors although exceptions do exist including infection exposure in acute lymphoblastic leukaemia (ALL), maternal drug and radiation exposure in utero, as well as environmental radiation exposures during childhood [16,17]. In contrast, childhood embryonal tumours often arise as a result of abnormal tissue embryogenesis, and as technologies have improved, have increasingly been found to occur on the background of a combination of tissue susceptibility linked to developmental growth rates reflected in epigenetic changes in host tissues and increased genetic predisposition [14]. The age distribution of different types of childhood cancers has been increasingly studied as part of the molecular characterisation of tumour for prognostication of risk groups. Peaks in incidence of tumour sub-type correlate with specific developmental / age eras, which in the major childhood brain tumour types in the cerebellum (medulloblastoma, ependymoma and astrocytoma) have been shown to correlate with steps in embryogenesis of specific anatomical brain structures [18] There are other examples of this phenomenonology. Study of this age / developmental stratification of tissue vulnerability to cancer development offers a framework therefore for understanding the timing of markers as candidates for steps in early oncogenesis and prognostication for targeted therapy. These steps have been studied intensively for the latter purpose but have not, as yet, been systematically studied for the former [19]. From this evidence therefore there seems to be every reason to predict that there is time to predict whether a child will develop cancer with the right test, at the right time, during their childhood.

4. Surveillance, screening and enhancing awareness of childhood cancer will not lead to better outcomes

Childhood cancer at presentation threatens immediate loss of life and acquired disability with rapidly advancing symptoms. This justifies the need for rapid access to life saving interventions to stabilise tumour-

related threats of severe anaemia, infectious, haemorrhagic and metabolic risks, physical threats of tumour masses causing raised intracranial pressure, as well as facial, cervical, thoracic, abdominal, genital, spinal and bone and soft tissue expansive / invasive / compressive symptoms [20,21] Earlier intervention offers prevention or early reversal of malnutrition, pain and support for the patient and their family with information and preservation / restoration of access to peer group activities for the young patient in education and training. The earlier the diagnosis, the greater the opportunity to prevent or relieve these immediate risks. Earlier detection also offers down staging of tumours to smaller less disseminated tumours suitable for less intensive treatment strategies and enhanced long term cure rates. It cannot offer, with current knowledge, downgrading of tumours to less aggressive / more sensitive phenotypes with current therapies. It may offer the identification of markers for innovative targeted therapies applied at a time when the tumour is at an early stage of genesis and a minimised bulk of disease [22–24]

In considering how surveillance and screening for childhood cancer could work, we will describe examples of evidence to support current practice of targeted surveillance of at risk children (See supplementary materials) and their families. We will go on to consider how population screening for biomarkers indicating the presence of pre-malignant or malignant disease could be introduced in line with newborn screening. Both these approaches require a persistent effort to enhance and sustain public and professional awareness of the risks and symptoms of childhood cancer to complement the targeted approaches to surveillance and population screening.

5. Surveillance for inherited germline genetic variation

Traditionally, testing for cancer predisposition syndromes has been triggered when clinical details such as a positive family history, phenotypic clinical features and chromosomal abnormalities are identified as part of diagnostic testing of clinical abnormalities in early life. The wider use of genomic testing has shown that such approaches will underperform [25] as such mutations are now being recognised independent of clinical and historical features in an increasing proportion of childhood cancers. The range of predisposing germline mutations in children presenting with cancer is expanding, with reports of 4–10 %, overall, and 50–80 % in certain cancer types (e.g. Retinoblastoma, Adrenocortical carcinoma, Choroid Plexus Carcinoma, Pleuropulmonary Blastoma)[26,27]. A contemporary list of recognised predisposition syndromes and the tumour types where imaging surveillance is recommended is shown in Table A (Supplementary Materials).

Surveillance strategies depend upon the tumour types being anticipated. For leukemias, blood count and marrow surveillance is used but the speed of acute leukaemia evolution can sometimes be rapid with children presenting symptomatically between clinic visits. Clinical surveillance with parental or clinician examination +/- imaging for solid tumours is established practice in selected situations but there is currently a varied approach as to who has responsibility for its coordination between geneticists, oncologists, organ specialists, imaging specialists and paediatricians. Consensus protocols are emerging to act as guidance [22]. Public and professional awareness programmes to disseminate this enhanced clinical standard of practice are needed in parallel with awareness programmes of cancer symptomatology. Where there is the greatest motivation is when targeted treatments are available and summarised in Table 1.

Increased routine testing of children with cancer for mutations in predisposition genes is identifying additional individuals/family members at increased cancer risk, including those with pathogenic/likely pathogenic (P/LP) variants, who are now considered eligible for surveillance. Currently, data surrounding the risks for these individuals is sparse, limited by understanding of the significance of these variants in the normal population. There is a risk of over estimating cancer risks when studied within families identified with cancers [6,26]. The anticipated move towards widespread whole genome sequencing, accompanied by rapid advances in machine learning suggest that tools to integrate multiple variants into a personalised composite risk score could be developed as part of the research initiative [26].

We conclude that the established practice of surveillance of predisposition states provides ample evidence that efforts to detect cancer in childhood earlier are already justified and growing experience will contribute important information about patterns of tumour development under observation that is not currently available when, for the majority of cases, they present acutely. Extension of this approach to whole population screening will become the next step to be justified by this growing clinical and research evidence [28]

Table 1
Predisposition groups with targeted interventions in practice, under trial or proposed adapted from Brodeur et al. [22] (See supplementary materials).

Predisposition group	Surveillance method	Intervention proposals / practice
Li-Fraumeni Syndrome (LFS)	LFS (*TP53*) Whole body MR surveillance	TP53 targeted therapy trials
Neurofibromatoses	NF1 optic pathway glioma vision and imaging surveillance NF2 acoustic neuroma hearing and imaging surveillance	Chemotherapy and MAPKinase inhibitors trials to prevent vision loss Bevacizumab (Avastin) to prevent hearing loss
Overgrowth syndromes/ Familial Wilms tumour	Wilms tumour abdominal examination and imaging surveillance	Chemotherapy for nephroblastomatosis.
Neural tumour syndromes	RB1 newborn screening & lifelong whole body imaging for sarcoma. Tuberous Sclerosis imaging brain, kidney & lung Gorlin's syndrome surveillance for skin, jaw and brain tumours	Ocular laser therapy, ocular resection mTOR inhibitor (Everolimus). Surgical techniques, topical therapies for skin tumours, trials of hedgehog pathway inhibitors and smoothened antagonists
GI cancer syndromes	CMMRD / Lynch syndrome: imaging surveillance	Checkpoint inhibitors
Neuroendocrine syndromes	MEN syndromes clinical and imaging surveillance	Pre-emptive thyroidectomy
Leukemia predisposition state	ALL pre-disposition screening with blood counts BCR-ABL translocation with ALL and CML Down syndrome / TAM Myelodysplasia	Microbiome targeting trials under consideration Tyrosine kinase inhibitors Early modified chemotherapy Stem cell transplant
Miscellaneous	DICER 1 syndrome surveillance of lung, kidney, ovaries, and brain for tumour formation.	Trials of tyrosine kinase inhibitors, mTOR inhibitors, and PARP inhibitors

Abbreviations: AML, acute myeloid leukemia; GI, gastrointestinal; CMMRD, congenital mismatch repair syndrome.

6. Population screening for pre-malignant or malignant disease

Population screening as currently proposed would most likely be based initially upon analysis of newborn blood samples searching for sporadic or inherited mutations affecting developmental tissues that are recognised as contributory to the risk of cancer development in childhood [18,19,29,30,31]). In addition to DNA mutations, changes in DNA methylation patterns and copy number aberrations as well as the impact of the in-utero environment and variation in immune response are considered to contribute to cancer development. How the detection of such patterns of methylation in early life samples remains to be understood [19,26,31]. On the one hand, it is known that DNA methylation patterns change during fetal development and over the first year of life

[32]. Whilst on the other hand, aberrant DNA methylation patterns are strongly associated with some paediatric brain tumours such as ependymoma and diffuse midline gliomas [19]. The aim of any screening programme would be to offer a structured way of assuring the majority of the childhood population that cancer is not anticipated, whilst identifying a minority for whom targeted surveillance with further blood testing, clinical or imaging surveillance is recommended during specific periods of their childhood.

In proposing such a screening strategy it must be admitted that previous attempts to screen for childhood cancers produced unexpected results. Screening programmes for neuroblastoma in Germany, Japan, Quebec, the UK and French regions in the 1990s found no evidence that population screening reduced mortality, and indeed it led to an overall increase in the incidence of favourable, early stage, regressive neuroblastomas deemed never to be a clinical problem[33,34]. There was no increase in the detection of children with advanced stage disease with poor prognosis. Since the 1990s, biological understanding and marker technology has changed and the range of testing options expanded. This experience highlights the importance for any research initiative in screening to select the right marker and the timing of its detection and interpretation within the context of tissue development, familial risk and other clinical factors. (Other examples are described in supplementary materials)

7. The risks of screening might be unacceptable to families and healthcare professionals

Understanding why children develop cancer, how it can be prevented and speeding up the processes of getting diagnosed and starting treatment have been identified as key priorities by patients, carers and professional working with children with cancer in UK national consensus discussions [35] and globally within "The Global Initiative for Childhood Cancer launched by the World Health Organisation (WHO) [36]. These consensus statements provide clear justification to prioritise accelerating diagnosis for children with cancer across all health systems. The issues of consent for parents of the unborn child, infant and the individual later in childhood may conflict with the rights of the maturing young person to consent to being informed of their lifetime risk of cancer. There are the risks of false negative and positive results of screening and the consequences of the stress of surveillance programmes on wellbeing of children and their families, which need to be evaluated. The acceptability of such programmes will depend on the populations being screened, their culture and previous health experiences [37]. Whilst a penetrance of 5 % has been seen to justify population screening in metabolic conditions, the meaning of this number and its justification in childhood cancer is unclear and needs further evaluation with knowledge of the multiple factors involved [6,26].

8. Is childhood cancer screening justified economically?

The risks for children developing malignancy, coupled with the associated risks of mortality, acquired disability or morbidity from the tumour or its treatment are significant burdens for health systems which, as yet, have not been fully evaluated across economic groups of countries [9,38] . The shock for families to confront the threat of their child's potentially shortened lifespan and the high treatment costs for them and the health systems justify a fresh look at ways that these diseases are diagnosed in society [7]. It could be anticipated that screening would initially be introduced and evaluated in high income countries (HIC) and justified by the economic impact in their high cost systems. However, the economic impact of screening and surveillance in low and middle income countries (LMIC) would need to be built in to the research initiatives as the population impact of successful interventions could be far greater [39,40].

The WHO launched its Global Initiative for Child Cancer in 2018 with the joint goal of increasing survival to at least 60 % by 2030 while reducing suffering and improving quality of life for children with cancer globally [36,39]. The top priority in this programme is making the diagnosis early enough that therapy can be offered with curative intent. It has been proposed that investment in developments in childhood cancer health interventions offers a tripling of return in investment by the increase in survival [39]. In LMICs, improving the cancer detection rate and inclusion of children in funded treatment programmes represents an aspirational objective. In HICs, there is also a strong motive to further improve outcomes for childhood cancers. Preliminary modelling using survival alone as an end point for a newborn screening test identified the potential benefit on survival rates and a strong association between the cost of the test and the health economic impact on life years. What has not been studied is the impact on disability related to acquired brain injury, orthopaedic disability and lifelong endocrine replacement therapy and the associated effects of late mortality and morbidity[28].

9. What do we propose?

A range of research reports are already exploring theoretical and practical aspects of investigating and introducing interventions to screen for specific tumours at birth and the possibility for intervening in developmental disorders in early life [27,28,41,42,43]. They suggest that the health economics of such early interventions in rare childhood conditions are considered affordable to health systems. Mullen at al in their review [6] compared the historical Wilson and Jungner's screening criteria [44] for neuroblastoma and retinoblastoma against those of cervix, breast and colorectal cancer, where screening is established in adulthood. Individually neuroblastoma and retinoblastoma are identified in the two lowest population incidence groups with low levels of evidence for impact on survival rates, understanding of natural history and early stage of disease recognition compared to the adult cancer comparators. Together these are interpreted as not meeting the historic requirements for screening. We propose that by considering the cumulative age incidence of all childhood cancers together, coupled with the global survival and disability rates expressed over the life time at risk for children, that Wilson and Jungener's criteria would be satisfied now and further enhanced by research directed at optimizing the timing and selection of testing strategies, which, as they are developed, could be assessed for their acceptability, feasibility and risks within health system. These adaptations to the historical criteria to meet the needs of children would be in line with other health economic judgements of the value of health interventions in early life that have been accepted [45].

Components to support the development of such a research strategy (Fig. 2) could include:

1) an international collaboration to prioritise strategies and share learning from surveillance programmes already in practice on outcomes for known predisposition syndromes and genetic variants of uncertain risk.
2) The establishment of anonymised linked population cohort studies collecting clinical data and samples from pregnant mothers and their children, with ethically justified access to biomarker samples from placenta, cord blood or heel prick at birth. Such studies would act as a denominator for studies of specific markers and for studies of targeted patient populations.
3) Population-wide symptom awareness programmes would be required to complement bio-genetic screening / surveillance testing.
4) Strong patient and public representation and systematic evaluation of risks and benefits of screening on psychological as well as physical health outcomes.
5) Health economic analysis built into trial designs of any screening applicable in HIC and LMIC.

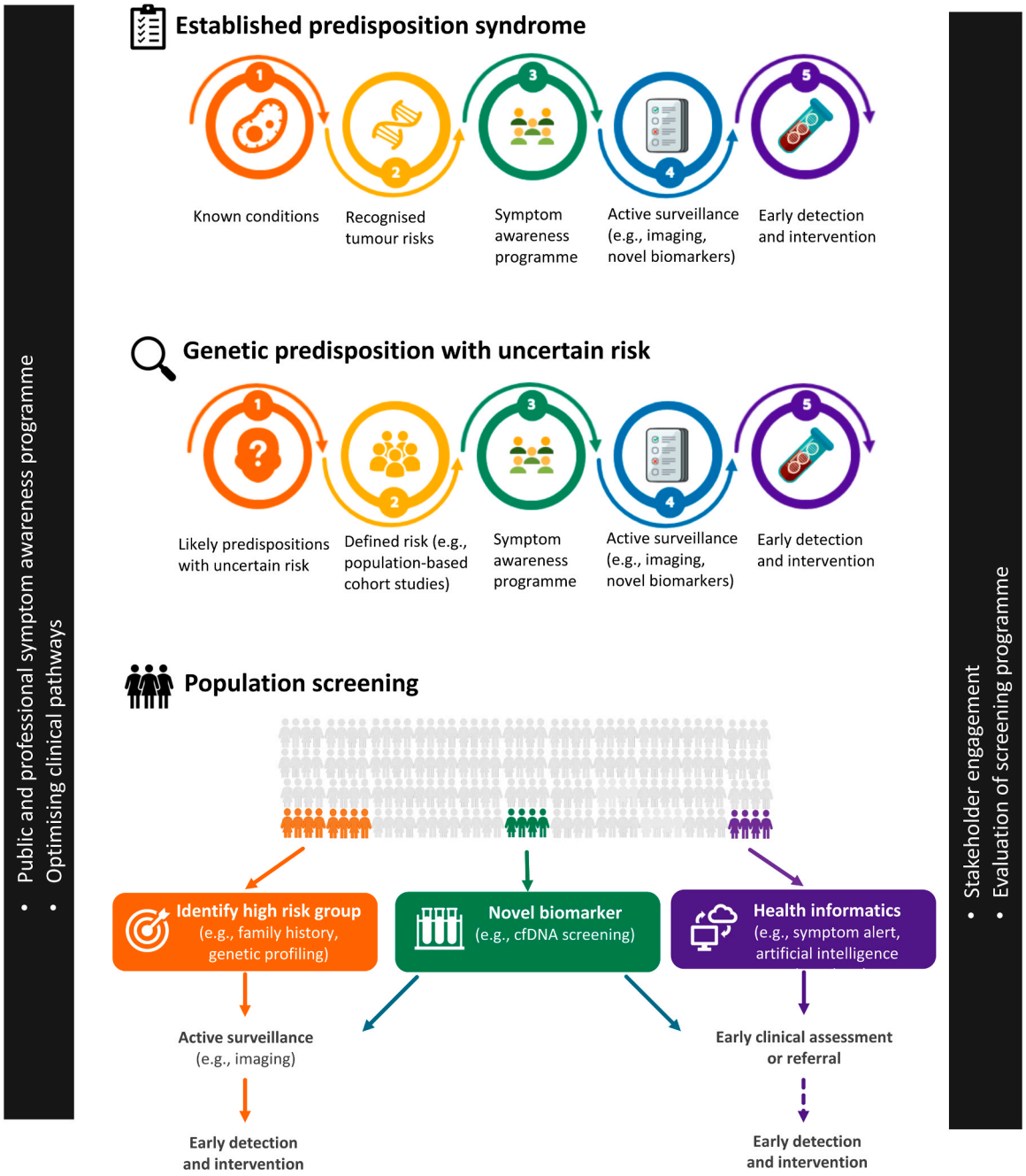

Fig. 2. Potential approaches to surveillance and screening. Surveillance pathway development in established cancer predisposition syndromes and potential route of developing future surveillance for. increasingly genetic variants of uncertain significance. Potential approaches for population screening to improve early detection of childhood cancer. Common themes of promoting symptom awareness across approaches. All approaches should be developed in partnership with stakeholders including, patients, families, primary care, genetics and oncology services with regular review and monitoring of impact.

Funding

Dhurgshaarna Shanmugavadivel (DS) has been funded by the NIHR (DRF-2018–11-ST2–055) and now funded by the CCLG.

JoFen Liu was funded by the Children's Brain Tumour Research Centre at University of Nottingham and is now funded by Childrens Cancer and Leulaeemia Group (CCLG)

Ashley Gamble is CEO for the Childrens Cancer and Leulaeemia Group (CCLG)

Chris Halsey is funded by Cancer Research UK (Programme Foundation Award) (DRCPFA-Nov21\100001) (CH)

Dr John Apps (JA) is funded by the University of Birmingham and Birmingham Women's and Children's Hospital NHS Foundation Trust. He was previously funded by an NIHR Academic Clinical Lectureship through the University of Birmingham. JA currently receives research funding from the Little Princess Trust, Birmingham Children's Hospital Charity, Help Harry Help Others and the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the University, NHS, the NIHR or the Department of Health.

Ms Kathy Oliver (KO) is Chair and Co-Director of the International Brain Tumour Alliance (IBTA) (www.theibta.org) and Kathy Oliver Consulting

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2024.100191.

References

[1] S. Brown, M. Castelli, D.J. Hunter, J. Erskine, P. Vedsted, C. Foot, et al., How might healthcare systems influence speed of cancer diagnosis: a narrative review, Soc. Sci. Med 116 (100) (2014) 56–63.
[2] D. Crosby, S. Bhatia, K.M. Brindle, L.M. Coussens, C. Dive, M. Emberton, et al., Early detection of cancer, Science 375 (6586) (2022) eaay9040.
[3] A. Pulumati, A. Pulumati, B.S. Dwarakanath, A. Verma, R.V.L. Papineni, Technological advancements in cancer diagnostics: improvements and limitations, Cancer Rep. 6 (2) (2023) e1764.
[4] T.P. Hanna, W.D. King, S. Thibodeau, M. Jalink, G.A. Paulin, E. Harvey-Jones, et al., Mortality due to cancer treatment delay: systematic review and meta-analysis, BMJ 371 (2020) m4087.
[5] W.D. Joo, I. Visintin, G. Mor, Targeted cancer therapy–are the days of systemic chemotherapy numbered? Maturitas 76 (4) (2013) 308–314.
[6] C.J.R. Mullen, R.D. Barr, E.L. Franco, Timeliness of diagnosis and treatment: the challenge of childhood cancers, Br. J. Cancer 125 (12) (2021 Dec 7) 1612–1620.
[7] J. Carlton, H.J. Griffiths, A.M. Horwood, P.P. Mazzone, R. Walker, H.J. Simonsz, Acceptability of childhood screening: a systematic narrative review, Public Health 193 (2021) 126–138.
[8] W.J. Ungar, Assessing value in child health, Children 8 (11) (2021).
[9] Kirsten K. Ness, Melissa M. Hudson, Jill P. Ginsberg, Rajaram Nagarajan, Sue C. Kaste, Neyssa Marina, John Whitton, Leslie L. Robison, James G. Gurney, Physical performance limitations in the childhood cancer survivor study cohort, ©, J. Clin. Oncol. 27 (2009) 2382–2389.
[10] R. Atun, N. Bhakta, A. Denburg, A.L. Frazier, P. Friedrich, S. Gupta, et al., Sustainable care for children with cancer: a Lancet Oncology Commission, Lancet Oncol. 21 (4) (2020) e185–e224.
[11] Z.J. Ward, J.M. Yeh, N. Bhakta, A.L. Frazier, R. Atun, Estimating the total incidence of global childhood cancer: a simulation-based analysis, Lancet Oncol. 20 (4) (2019) 483–493.
[12] Taeubner, J., Wieczorek,D., Yasin,L.,& Brozou,T. Penetrance and Expressivity in Inherited Cancer Predisposing Syndromes. Trends in Cancer, Volume 4, Issue 11, 718-728.
[13] D.A. Walker, Helping GPs to diagnose children's cancer, Br. J. Gen. Pract. 71 (705) (2021) 151–152, https://doi.org/10.3399/bjgp21X715241.
[14] P.J. Scotting, D.A. Walker, G. Perilongo, Childhood solid tumours: a developmental disorder, Nat. Rev. Cancer 5 (6) (2005) 481–488.
[15] J.G. Loeber, D. Platis, R.H. Zetterström, S. Almashanu, F. Boemer, J.R. Bonham, et al., Neonatal screening in Europe revisited: an ISNS perspective on the current state and developments since 2010, Int J. Neonatal Screen 7 (1) (2021).
[16] Kattner P., Strobel H., Khoshnevis N., Grunert M., Bartholomae S., Pruss M., et al. Compare and contrast: pediatric cancer versus adult malignancies. Cancer and Metastasis Reviews.
[17] M. Greaves, V. Cazzaniga, A. Ford, Can we prevent childhood Leukaemia? Leukemia 35 (5) (2021) 1258–1264.
[18] K. Okonechnikov, P. Joshi, A. Korshunov, et al., Mapping pediatric brain tumors to their origins in the developing cerebellum, Neuro-Oncol. Volume 25 (Issue 10) (October 2023) 1895–1909, https://doi.org/10.1093/neuonc/noad124.
[19] M. Filbin, M. Monje, Developmental origins and emerging therapeutic opportunities for childhood cancer, Nat. Med 25 (3) (2019) 367–376.
[20] https://www.rcemlearning.co.uk/foamed/an-approach-to-paediatric-oncological-presentations-in-the-emergencydepartment/
[21] J. Theis, Oncologic emergencies in pediatric patients: what oncology nurses need to know, Oncology 36 (7) (2014) 2–4.
[22] G.M. Brodeur, K.E. Nichols, S.E. Plon, J.D. Schiffman, D. Malkin, Pediatric cancer predisposition and surveillance: an overview, and a tribute to alfred G. Knudson Jr, Clin. Cancer Res 23 (11) (2017) e1–e5.
[23] Y. Liu, J. Klein, R. Bajpai, L. Dong, Q. Tran, P. Kolekar, et al., Etiology of oncogenic fusions in 5,190 childhood cancers and its clinical and therapeutic implication, Nat. Commun. 14 (1) (2023) 1739.
[24] E.A. Sweet-Cordero, J.A. Biegel, The genomic landscape of pediatric cancers: implications for diagnosis and treatment, Science 363 (6432) (2019) 1170–1175.
[25] J. Zhang, M.F. Walsh, G. Wu, M.N. Edmonson, T.A. Gruber, J. Easton, et al., Germline mutations in predisposition genes in pediatric cancer, N. Engl. J. Med 373 (24) (2015) 2336–2346.
[26] C.P. Kratz, M.C. Jongmans, H. Cave, K. Wimmer, S. Behjati, L. Guerrini-Rousseau, et al., Predisposition to cancer in children and adolescents, Lancet Child Adolesc. Health 5 (2) (2021) 142–154.
[27] J.J. Bakhuizen, S.M.J. Hopman, M.I. Bosscha, C.J. Dommering, M.M. van den Heuvel-Eibrink, J.A. Hol, et al., Assessment of cancer predisposition syndromes in a national cohort of children with a neoplasm, JAMA Netw. Open 6 (2) (2023) e2254157.
[28] J.M. Yeh, N.K. Stout, A. Chaudhry, K.D. Christensen, M. Gooch, P.M. McMahon, et al., Universal newborn genetic screening for pediatric cancer predisposition syndromes: model-based insights, Genet Med 23 (7) (2021) 1366–1371.
[29] Y. Liu, J. Klein, R. Bajpai, L. Dong, Q. Tran, P. Kolekar, et al., Etiology of oncogenic fusions in 5,190 childhood cancers and its clinical and therapeutic implication, Nat. Commun. 14 (1) (2023) 1739.
[30] L. Zhu, D. Finkelstein, C. Gao, L. Shi, Y. Wang, D. Lopez-Terrada, et al., Multi-organ mapping of cancer risk, Cell 166 (5) (2016) 1132–1146, e7.
[31] O. Alonso-Luna, G.E. Mercado-Celis, J. Melendez-Zajgla, M. Zapata-Tarres, E. Mendoza-Caamal, The genetic era of childhood cancer: identification of high-risk patients and germline sequencing approaches, Ann. Hum. Genet 87 (3) (2023) 81–90.
[32] E. Wikenius, V. Moe, L. Smith, E.R. Heiervang, A. Berglund, DNA methylation changes in infants between 6 and 52 weeks, Sci. Rep. 9 (1) (2019) 17587.
[33] F.H. Schilling, C. Spix, F. Berthold, R. Erttmann, N. Fehse, B. Hero, et al., Neuroblastoma screening at one year of age, N. Engl. J. Med 346 (14) (2002) 1047–1053.
[34] W.G. Woods, R.N. Gao, J.J. Shuster, L.L. Robison, M. Bernstein, S. Weitzman, et al., Screening of infants and mortality due to neuroblastoma, N. Engl. J. Med 346 (14) (2002) 1041–1046.
[35] (https://www.jla.nihr.ac.uk/priority-setting-partnerships/childrens-cancer/top-10-priorities.htm
[36] https://www.who.int/initiatives/the-global-initiative-for-childhood-cancer
[37] W.N. Gray, L.J. Szulczewski, S.M. Regan, J.A. Williams, A.L. Pai, Cultural influences in pediatric cancer from diagnosis to cure/end of life, J. Pedia Oncol. Nurs. 31 (5) (2014) 252–271.
[38] H.V. Russell, J. Panchai, Helena vonVille, Luisia Franzini, J.Michael Swint, Economic evaluation of pediatric cancer treatment: a systematic literature review, Pediatrics 131 (1) (2013) e273–e287.
[39] R. Atun, N. Bhakta, A. Denburg, A.L. Frazier, P. Friedrich, S. Gupta, et al., Sustainable care for children with cancer: a Lancet Oncology Commission, Lancet Oncol. 21 (4) (2020) e185–e224.
[40] A. Fung, S. Horton, V. Zabih, et al., Cost and costeffectiveness of childhood cancer treatment in low income and middle-income countries: a systematic review, BMJ Glob. Health 4 (2019) e001825, https://doi.org/10.1136/bmjgh-2019-001825.
[41] A. Villani, A. Shore, J.D. Wasserman, D. Stephens, R.H. Kim, H. Druker, et al., Biochemical and imaging surveillance in germline TP53 mutation carriers with Li-Fraumeni syndrome: 11 year follow-up of a prospective observational study, Lancet Oncol. 17 (9) (2016) 1295–1305.
[42] A. Gerrish, E. Stone, S. Clokie, J.R. Ainsworth, H. Jenkinson, M. McCalla, et al., Non-invasive diagnosis of retinoblastoma using cell-free DNA from aqueous humour, Br. J. Ophthalmol. 103 (5) (2019) 721–724.
[43] R.T. Sundby, A. Pan, J.F. Shern, Liquid biopsies in pediatric oncology: opportunities and obstacles, Curr. Opin. Pediatr. 34 (1) (2022) 39–47.
[44] J.M.G. Wilson, G. Jungner, Principles and practice of screening for disease. Public health papers, World Health Organization, Geneva, 1968.
[45] https://www.nice.org.uk/news/articles/nice-approves-life-changing-gene-therapy-for-treating-spinal-muscular-atrophy